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VISCERAL KAPOSI'S DISEASE

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OUR INTEREST in Kaposi's disease was first aroused by a case of sudden death, diagnosed clinically as due to hypertensive heart disease, that one of us (Tedeschi) had the opportunity to study several years ago. Postmortem examination revealed spongy bluish red nodules in the liver, the left kidney and the small bowel. Microscopically, these nodules were found to have a structure similar to that ascribed to cutaneous Kaposi's disease. Since cutaneous manifestations were lacking at the time of the autopsy and since there was no mention of any in the clinical history, the diagnosis of visceral Kaposi's disease was not felt to be justified and the case was filed as one of "systemic angioreticulosis," the emphasis being placed thus on the most striking pattern in the hepatic, intestinal and renal nodules: a disorderly proliferation of reticulum cells along various lines, with development of vascular channels.

Many years later (1945) we were confronted with an identical structural pattern in a mediastinal mass, again characterized by an intimate new growth of vascular structures and young mesenchymal cells, in a woman dying of myelogenous leukemia. Although in this case, also, the structural characteristics of the mediastinal mass closely resembled those of cutaneous Kaposi's disease, we felt that this diagnosis was not justified, and the mass was classified as "angioreticuloma."

The present report was prompted by a third similar case which was recently brought to our attention: A boy died of intestinal intussusception who, in the complete absence of cutaneous lesions, showed lymph-glandular, splenic, intestinal and hepatic lesions, the structure of which again simulated the patterns of cutaneous Kaposi's disease. At the time this case was being studied some articles had already appeared which discussed the possibility of "visceral Kaposi's disease" in which the process may remain confined to the internal organs or in which

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the visceral manifestations may precede the cutaneous lesions. The diagnosis of "visceral Kaposi's disease" was made for the third case, and this, together with the two previous similar cases, is reported here, with a further discussion of this new aspect of Kaposi's disease.

REVIEW OF LITERATURE

Medical literature contains numerous references to this uncommon condition described by Moritz Kaposi [1] and labeled first as "idiopathic multiple pigmented sarcoma" (1872), then as "sarcoma idiopathicum multiplex hemorrhagicum" (1894) and currently as Kaposi's sarcoma or multiple idiopathic hemorrhagic sarcoma.

Incidence and Localization.—Some hundred cases of the disease recorded in the literature enabled us to make certain well established generalizations: that the incidence is greater in males, only 5.99 per cent of the patients in the 434 cases described up to 1939 having been females (Choisser and Ramsey [2]); that the prevailing distribution of the disease is among the populations of Eastern Europe and Northern Italy, though no part of the world lacks representation; that the peak of frequency is in the fifth, sixth and seventh decades of life; that the condition occasionally develops in several members of the same family (Greco [3]), and that patients of the white races predominate over those of the Negro race.

The extremities, the face and the trunk are the most frequent sites of cutaneous localization. Contrary to Kaposi's expectation, secondary involvement of the internal organs is not frequent, occurring only in about 10 per cent of the cases; spontaneous regression of the nodules has been noted many times, and the disease is no longer regarded as invariably fatal.

Among the later developing visceral localizations, the most frequent is the gastrointestinal tract, including all portions from the mouth to the rectum; however, practically all organs may be involved by the process. Diarrhea, gastrointestinal hemorrhage and hemorrhagic effusion into a serous sac have been occasionally recorded in connection with the intestinal and serosal localizations.

Pathologic Aspects.—Among the earliest manifestations of the disease, a swelling of the extremities, usually symmetric in distribution, has been reported and variously interpreted (Stats [4]; Mierzecki [5]; Hansson [6]). Blockage of lymph drainage was accounted for either by

1. Kaposi, M., cited by Kren.[8]
2. Choisser, R. M., and Ramsey, E. M.: Am. J. Path. **15**:155, 1939.
3. Greco, cited by Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, St. Louis, C. V. Mosby Company, 1939.
4. Stats, D.: J. Mt. Sinai Hosp. **12**:971, 1946.
5. Mierzecki, H.: Arch. f. Dermat. u. Syph. **165**:577, 1932.
6. Hansson, C. J.: Acta radiol. **21**:457, 1940.

infiltration of the lymphatic vessels or by involvement of the regional lymph glands (Dalla Favera[7]; Kren[8]; Aegerter and Peale[9]). In some other cases an explanation was found in coexistent dermic sclerotic changes in proximity to the cutaneous nodules; but a large group of cases still remains in which no apparent cause could be found for the condition.

Another early development in the disease is the more or less general lymphadenopathy affecting both superficial and deep lymph nodes and noticeable at a time when the cutaneous lesions are not yet manifest or are so limited in extent or so indefinite in character as to be easily overlooked or misinterpreted. The enlargement of the lymph nodes does not necessarily indicate that they are involved by the process. In some of Dalla Favera's cases[7] the only detectable change was a thickening of the fibrous connective tissue stroma of the lymph glands. Hyperplasia of reticulum cells was thought by Dörffel[10] to account for the condition. A similar change was described by Greppi and Bettoni,[11] while in Goldschlag's cases[12] the pattern was that of a chronic nonspecific inflammatory process. Plasma cell infiltration, the presence of histiocytic phagocytes containing iron pigment and a moderate thickening of the stroma of the lymph glands led to a similar interpretation in the cases of MacKee and Cipollaro.[13] It is difficult at present to discuss the significance of these changes; one possibility is that they may represent an aspecific inflammatory reaction; the other possibility is that they may represent early stages of the development of the disease process.

Besides the enlargement of the lymph nodes, Stats[4] has recently called attention to the concomitant enlargement of the spleen. This organ weighed 1,340 Gm. in the case of Usseglio and associates,[14] 1,000 Gm. in a case observed by Symmers[15] and over 700 Gm. in not a few instances recorded (Stats[4]). In some cases the presence of tumor nodules was found to be responsible for the condition (Symmers[15]; Paolini[16]), but in a considerable number of other cases no

7. Dalla Favera, G. B.: Arch. f. Dermat. u. Syph. **109**:387, 1911.

8. Kren, O.: Sarcoma idiopathicum haemorrhagicum, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, vol. 12, p. 891.

9. Aegerter, E. E., and Peale, A. R.: Arch. Path. **34**:413, 1942.

10. Dörffel, J.: Arch. Dermat. & Syph. **26**:608, 1932.

11. Greppi, E., and Bettoni, I.: Arch. Ist. biochim. ital. **4**:403, 1932.

12. Goldschlag, F.: Dermat. Wchnschr. **100**:204, 1935.

13. MacKee, G. M., and Cipollaro, A. C.: Am. J. Cancer **26**:1, 1936.

14. Usseglio, G.; Zambelli, E., and Paolino, W.: Gior. d. r. Accad. di med. di Torino **101**:404, 1938.

15. Symmers, D.: Arch. Path. **32**:764, 1941.

16. Paolini, R.: Rassegna internaz. di clin. e terap. **8**:514, 1927.

evidence of specific splenic involvement could be noticed. In the case of Greppi and Bettoni [11] the findings included a "hemolytic spleen" with marked "arterial hyperemia"; in the case of Usseglio and associates [14] the enlargement of the organ appeared to be due mostly to hyperplasia of macrophagic histiocytes, many of which contained red blood cells, while in the case of Stats [4] it was due to hyperplasia of reticulum cells.

Changes comparable to those in the spleen were occasionally noted in specimens of marrow obtained by sternal aspiration. Active hyperplastic marrow was found by Stats [4] in 2 cases, and Bertaccini [17] reported an increase of reticuloendothelial cells and monocytes in 2 other cases. In these 2 cases and in 2 others reported by the same author there were concomitant deviations from the normal in the hemogram of the peripheral blood, mainly a marked increase of the monocytes. Monocytosis of a considerable degree was observed also in some of the cases of Dörffel [10] and Bruns.[18] Flarer [19] recognized as many as 60 per cent abnormal monocytes in the peripheral blood, showing a marked shift toward the cells of the lymphomonocytic series. As for the findings in the spleen and in the lymph nodes, the changes in the marrow and in the peripheral blood were regarded by some as evidence of the widespread involvement of the reticuloendothelial system. The conception of the systemic nature of Kaposi's disease and its relation to lymphoblastoma and reticuloendothelioma have been emphasized lately in papers discussing cases in which Kaposi's disease developed concomitantly with mycosis fungoides (Lane and Greenwood [20]), or with lymphatic leukemia (Cole and Crump [21]), or with Hodgkin's disease or lymphoblastoma (Gilchrist and Ketron [22]).

Histologic Observations.—The variable histologic structure of Kaposi's morphologic unit has presented problems the solution of which has baffled many investigators. The 23 different names applied from time to time to the increasing number of cases (MacKee and Cipollaro [13]) are indicative of the lack of agreement as to the point of origin of the growth.

We are indebted to Dörffel [10] for a fine description of the changes throughout the development of Kaposi's nodule. Among the patterns characteristic of the earliest stages, the author stresses a network of blood capillaries surrounded by a thick mantle of young mesenchymal cells embedded in the meshes of a thin interlacing of argentaffin fibers.

17. Bertaccini, G.: Gior. ital. di dermat. e sif. **80**:631, 1939.

18. Cited by Bertaccini.[17]

19. Flarer, F., cited by Bertaccini.[17]

20. Lane, C. G., and Greenwood, A. M.: Arch. Dermat. & Syph. **27**:643, 1933.

21. Cole, H. N., and Crump, E. S.: Arch. Dermat. & Syph. **38**:283, 1920.

22. Gilchrist, T. A., and Ketron, L. W., cited by Highman, W. J., in discussion on Lane and Greenwood,[20] p. 654.

Sinus-like spaces lined by endothelial cells not unlike those found in the splenic tissue are present and are interpreted as the earliest attempt at formation of new blood vessels. Blocks or granules of iron pigment, either free or within macrophagic histiocytes, are noticeable, and their presence is explained by an escape of red blood cells into the tissue through the incompletely closed blood channels.

In a later stage, corresponding grossly to the "bright red nodule," the vascular network is still more striking, with many vessels and cavernous spaces, lined by one or more layers of endothelial cells, spreading in various directions in a fanlike fashion.

If the proliferation of blood vessels prevails in the process, the resulting pattern will be that of angioblastoma. If, instead, the cellular proliferation is predominant, the growth is likely to bear a striking resemblance to round cell or spindle cell sarcoma.

Spontaneous regression of newly formed nodules is explained on the basis of degenerative changes, shown by the cytoplasmic and nuclear vacuolation, the edema and the myxomatous change of the stroma, at times followed by attempted repair in the form of a proliferation of granulation tissue. These changes are not unlikely to be seen in concomitance with thrombotic changes in blood vessels or independent of them.

The conclusion that Dörffel [10] reached is that the cell type involved basically is the pluripotent cell of the reticuloendothelial system which, owing to its various developmental potentialities, is able to give rise to complex and unpredictable structures.

This conclusion has been accepted by a number of investigators (Guccione [23]; Flarer [19]; Choisser and Ramsey [2]), and Goldsmith,[24] in a recent article, did not hesitate to classify Kaposi's sarcoma as among the diseases of the reticuloendothelial system. The same view was expressed by Puhr,[25] who explained the formation of blood vessels in the growth by fusion and subsequent excavation of cells in which he recognized all the functional and morphologic characteristics of the reticuloendothelial cells. Greppi and Bettoni [11] reached a similar conclusion in discussing an unusual case of Kaposi's disease with extensive visceral manifestations and concomitant hemolytic splenomegaly. According to them, the involvement of the reticuloendothelial system in their case had manifested itself in the splenic district with an exaggeration of the hemocatheretic function proper to this organ, while elsewhere it had given rise to a neoplastic growth with the characteristics of Kaposi's disease.

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23. Guccione, F.: Arch. ital. di anat. e istol. pat. **5**:1, 1934.
24. Goldsmith, W. N.: Brit. J. Dermat. **56**:104, 1944.
25. Puhr, L.: Dermat. Wchnschr. **91**:1815, 1930.

Yet there is no unanimity concerning the origin of the process. Kren [8] doubted that the cells primarily involved are the reticuloendothelial cells and stated that the only substantial point in favor of this origin is the presence of cells provided with phagocytic power in the newly formed nodules. The unit of growth in Kaposi's disease, according to Symmers,[15] is the fibroblast, a cell which is able to maintain a low capacity of growth over a number of years and which may suddenly assume active proliferation ending with widespread destruction of tissues as in a spindle cell sarcoma.

Etiology.—Although microscopic studies have led to fairly general agreement as to the histologic features necessary to establish the diagnosis, in the present state of knowledge there is little agreement regarding the etiologic explanation of the condition. Some classify Kaposi's disease among the granulomas and others among the neoplasms. The opinion held by the majority in the past and still shared by some at present (Van Cleve and Hellwig [26]) is that there is an infectious agent of unknown origin attacking the entire vascular and perivascular system with the lesions assuming neoplastic characteristics in predisposed subjects and under certain conditions. Against this are the crucial experiments of Pack [27] and Choisser and Ramsey [28] who, using the injection method in human subjects, failed to elicit any sort of reaction.

Recalling Hodgkin's disease, for which a recent classification in subgroups has been found to be satisfactory both from the clinical and from the pathologic standpoint, one might also accept for Kaposi's disease the similar subdivisions proposed by MacKee and Cipollaro,[13] namely, inflammatory, granulomatous and neoplastic processes. Among the cardinal features of the inflammatory pattern the authors list engorgement of blood and lymph vessels, extravasation of red blood cells, and perivascular infiltration by round cells, connective tissue cells and plasma cells. Predominant features of the granulomatous pattern are the proliferation of hematic and lymphatic channels accompanied by pronounced hyperplasia of connective tissue cells. In the neoplastic pattern the picture varies according to the elements predominantly involved: If the hyperplastic-dysplastic process affects the blood vessels mainly, the picture will be that of hemangioblastoma; if, instead, the lymphatic vessels prevail in the growth, the picture will be that of lymphangioma or of a mixture of hemangioma and lymphangioma; fibroma, angiofibroma, angiosarcoma or spindle cell sarcoma may result from excessive and disorderly connective tissue cell proliferation.

The hypothesis of the systemic nature of Kaposi's disease has been advocated by many investigators. In discussing 4 cases in which

26. Van Cleve, J. V., and Hellwig, C. A.: Urol. & Cutan. Rev. **39**:246, 1935.
27. Pack, G. T.: J. M. Soc. New Jersey **34**:603, 1927.
28. Choisser, R. M., and Ramsey, E. M.: South. M. J. **33**:392, 1940.

anatomic and functional changes occurring in blood vessels were noticeable far beyond the Kaposi lesions, Santori [29] expressed the opinion that underlying the disease was a congenital or an acquired general debility of the vascular system. Bessone [18] arrived at a similar conclusion, and in 4 of his cases he was able to demonstrate capillary fragility as well as anatomic vascular defects. This was also noticed by Bertaccini,[17] who emphasized the abnormal appearance of the blood capillaries, which displayed thickness and hyalinosis of the walls both in proximity to and at a distance from the lesions. Along the same line is the explanation of Leigheb [30] in a case in which Kaposi's disease apparently followed an erythema from arsphenamine. Favre and Josserand ascribed Kaposi's disease to systemic angiomatosis without hesitancy.

It was assumed in the past by most students that the extracutaneous lesions in the disease were metastatic. This appeared to be justified by the fact that up to the time of Dörffel's paper [10] no case had been reported in which lesions of the skin were lacking. The literature since 1932 includes the reports of a few cases in which the involvement of the internal organs seems to have preceded the cutaneous manifestations, and even of some cases in which the cutaneous lesions were lacking altogether.

In Pearce and Valker's case [31] a nodule in the gum was noticeable several months before the skin became involved. Barringer and Dean [32] twice noted primary lesions on the glans penis. Van Cleve and Hellwig [26] and Goldschlag [33] reported cases in which the inguinal lymph nodes were primarily involved. Paolini [16] had a patient who complained of intestinal symptoms long before the appearance of the cutaneous manifestations. The pharynx and larynx were primarily involved in a case reported by Bilancioni.[34] In the patient of Greppi and Bettoni [11] the only apparent external manifestation was in the glans penis; later on the inguinal lymph nodes became involved, but no lesions of the skin developed during the year of illness prior to death. At autopsy the psoas muscles were extensively involved, and nodules were found in the lungs. In the case of Stats,[4] about fourteen months intervened between the onset of the illness, characterized by symmetric pitting edema of both lower extremities, and the appearance of circumscribed nodules in both legs.

Incidental involvement of the heart and pericardial sac, generally with absence of clinical symptoms, has been frequently recorded as

29. Santori, G.: Gior. ital. di dermat. e sif. **73**:782, 1932.
30. Leigheb, V.: Arch. ital. di dermat. e sif. **11**:461, 1935.
31. Pearce, C. T., and Valker, L. E.: Ohio State M. J. **32**:137, 1936.
32. Barringer, B. S., and Dean, A. L., Jr.: Tr. Am. A. Genito-Urin. Surgeons **28**:409, 1935.
33. Goldschlag, F.: Dermat. Wchnschr. **100**:204, 1935.
34. Bilancioni, G.: Rassegna internaz. di clin. e terap. **13**:1135, 1932.

among the visceral localizations of Kaposi's disease (Symmers [15]; Dillard and Weidman [35]; Stats,[4] cases 2 and 4). A primary and unique cardiac localization is more unusual. Almost simultaneously, in two independent papers, Weller [36] and Choisser and Ramsey [2] described 2 cases (which Stats suspects to be the same) of primary Kaposi's sarcoma of the right atrium of the heart, classified as angioreticuloendothelioma from the morphologic standpoint. Similar cases were described by da Cunha Motta,[37] and more recently Aegerter and Peale [9] have added another case in which the only apparent localization of the disease was in the right atrium of the heart. The identification of these cases as instances of Kaposi's disease was based on the close resemblance of the cardiac findings to those usually seen in association with the cutaneous manifestations of Kaposi's disease. Whether or not the cases deserve to be considered as such is one of the pertinent points of the present study.

ILLUSTRATIVE CASES

Case 1.—In North Italy a laborer aged 59 years was admitted to St. Anne's Hospital, Ferrara, Jan. 20, 1938. He was moribund and died after a few hours. The only information that could be obtained was that for a number of years he had had high blood pressure, frequent dizzy spells and symptoms of cardiac decompensation which had greatly limited his activities.

Necropsy.—The body was that of an obese, well developed white man who appeared to be somewhat older than the stated age of 59 years. The lips, the mucous membranes of the mouth and the nail beds of the fingers and the toes were deeply cyanotic, but no other significant changes could be detected by external examination of the body.

There was a large heart, of an estimated weight of 450 Gm., with marked hypertrophy of the left ventricle and severe sclerotic changes of the coronary arteries. There was much myocardial fibrosis, and scarring was noticeable in places. Both lungs were congested and edematous, but no areas of consolidation were found. The kidneys weighed 250 Gm. together and were granular in appearance, with atrophy both of cortex and of medulla, and with formation of cysts. Hyalinosis of glomeruli, arteries and arterioles was later observed in the microscopic sections, and the cause of death was attributed to cardiorenal arteriosclerotic disease.

In the course of the autopsy our attention was mainly attracted by the bluish red nodules present in various organs of the abdominal cavity. One of these nodules, 1.8 cm. in diameter, was in the liver. It was firm, elastic in consistency, smooth and glistening on the surface but spongy on the cut section owing to concameration of cavities of different sizes. Some of these cavities were empty, while others contained fluid blood. As there was no capsule, nor any formation resembling a capsule, circumscribing the nodule from the surrounding hepatic parenchyma, the limits between the two tissues were not clearly made out, the nodule blending smoothly into the hepatic tissue.

35. Dillard, C. I., and Weidman, F. D.: Arch. Dermat. & Syph. **1**:283, 1920.

36. Weller, G. L.: Ann. Int. Med. **14**:314, 1940.

37. da Cunha Motta, L.: An. Fac. de med. da Univ. de São Paulo (pt. 2) **17**: 627, 1941.

Another nodule the size of a large pea was embedded in the upper pole of the left kidney. Except for the smaller size it did not differ from the nodule in the liver. Approximately half of the nodule was fleshy and hemorrhagic, while the other half was firm, elastic, compact and somewhat variegated in color because of alternating grayish pink and yellow-tinged areas. The renal nodule also was not sharply demarcated from the surrounding tissue, merging at its borders into the renal parenchyma.

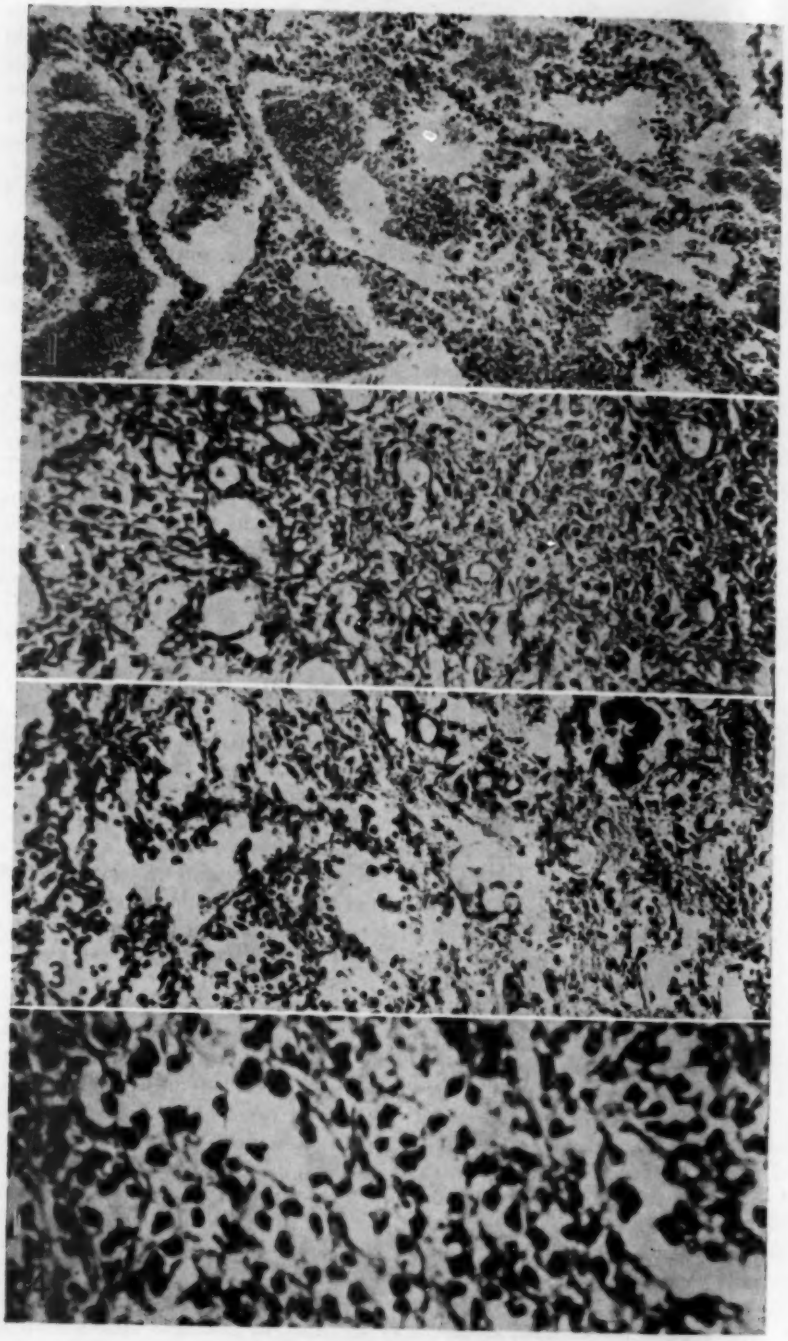
The third nodule was discovered in the small intestine, about 3 feet (91.5 cm.) from the ileocecal valve. Hemispheric in shape and the size of a small cherry, it bulged beneath the intestinal mucosa, which was smooth, glistening and otherwise not remarkable. On the cut section the central portion of the nodule looked like a sponge filled with blood, while at the periphery there was a condensation of tissue gently melting into the intestinal walls.

Microscopic Observations.—The microscopic sections from the nodule in the liver showed it to be composed of an interlacing of young connective tissue fibers, some of which, bending in a circular fashion, resulted in the formation of closed spaces (fig. 1). Some of these spaces were lined by a layer of flattened or fusiform cells regularly alined one after the other, which resembled in all respects the endothelial cells lining the blood and lymph vessels. Red blood cells were contained in some of these spaces, and other red blood cells lay in the surrounding tissue. Scanty connective tissue cells, either sparse or in small groups, could be seen here and there. Some of these cells, with large vesicular nuclei provided with nucleoli and basophilic cytoplasm, had the characteristics of reticulum cells. The majority, however, were spindle shaped, with swollen vesicular nuclei, and displayed all the attributes of young fibroblasts.

The structure of the nodule in the intestine differed somewhat from the structure of the hepatic nodule. The fundamental pattern was still that of thin-walled blood channels embedded in a fibrous connective tissue stroma, hyaline in places (fig. 2). Some of these channels were composed of a single lamella of regularly alined endothelial cells; some others, of an endothelial lamella lying on a thin layer of collagenous tissue. All these channels were greatly dilated, with sinuosities along the walls which here and there appeared surrounded by a scattering of cells, mostly fibroblasts and lymphocytes with occasional histiocytes. Well preserved red blood cells were present in the lumens of the blood channels, and more red blood cells, either sparse or in groups, were seen in the meshes of the surrounding fibrous connective tissue stroma. Granules of yellowish brown pigment were seen, mostly within large macrophagic histiocytes, and they were identified as iron granules in the sections stained by Turnbull's blue method.

The limits between the nodule and the surrounding intestinal submucosa appeared to be better defined in the microscopic sections than they had been to the naked eye, because of a palisade of connective tissue fibers in parallel arrangement all around the nodular formation. Yet even beyond this palisade of connective tissue fibers the vascular intestinal pattern appeared distorted. Groups of thin-walled engorged blood vessels stood out conspicuously, and in the absence of inflammatory changes or any other apparent pathologic condition the same disorderly arrangement could be noticed in tracts of small intestine at some distance from the nodule, giving the impression that the vascular defect had more extensive roots than one might have suspected at first.

The structure of the renal nodule was more complicated. It varied from area to area, yet the predominant feature was still that of sinus-like spaces lined by one or more rows of endothelial cells, not unlike the spaces and cells observed in the spleen (fig. 3). Between the spaces there was a fibrous-cellular stroma,



Figures 1 to 4

(See legends on opposite page)

abundant in some spaces and scanty in some others. Among the stroma cells two different cell types could be recognized. One type was a spindle-shaped or polygonal cell, with a large pale-stained nucleus, a fine chromatin network, one or two nucleoli and abundant cytoplasm. The other type was a small round or oval cell with a dark nucleus and a thin ring of cytoplasm. The chromatin was mostly condensed at the periphery of the nucleus, forming a distinct nuclear membrane. The surrounding cytoplasm was compact in some cells and finely vacuolated in some other cells. Short processes departed from the cellular outlines and showed a tendency to fuse together with similar processes of adjacent cells. These cells, which in many respects resembled the cells lining the sinuses, showed at times a spongy appearance due to abundant sudanophilic granules. In the areas in which the lipopessic cells were most numerous, a network of argentaffin fibers which surrounded almost every cell was shown by the silver-stained sections (Foot). Argentaffin fibers were also present elsewhere but were not so homogeneous in distribution, and the network pattern was disrupted at many points by large hemorrhagic infiltrates. Some of the hemorrhages were recent, others older, and a good deal of blood pigment could be recognized either free or in large mesenchymal cells.

Summary.—In a man aged 59 who died of cardiorenal arteriosclerotic disease, postmortem examination revealed in the liver, the left kidney and the small bowel bluish red spongy nodules which on microscopic examination were found to consist of blood-filled channels lined by endothelial cells in one or more rows. These channels were embedded in a fibrous-cellular stroma rich in reticulum cells and fibers, in young fibroblasts and in histiocytic macrophages containing blood pigment. The vascular tree at a certain distance from the intestinal nodule showed clear evidence of faulty development.

Case 2.—A 65 year old American-born woman was admitted to the Framingham Union Hospital Sept. 18, 1945, complaining of weakness, dysphagia and sore throat which had been present approximately one month and accompanied by loss of weight. One week previous to admission these symptoms became more severe, with elevation of temperature. There was no mention of serious illness in the past or in the family except for a brother who died of leukemia.

Examination at admission revealed an ill woman, extremely pale. Scattered all over the skin of the arms and the trunk there were numerous purpuric areas,

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Explanation of Figures 1 to 4

Fig. 1 (case 1, from the nodule in the liver).—Intercommunicating vascular spaces lined by endothelial cells lying on a thin ribbon of collagenous fibers. Lymphocytes and fibroblasts, either sparse or in groups, are noticeable in the intervening stroma. Ocular 5, objective 10.

Fig. 2 (case 1, from the nodule in the intestine).—Blood channels and sinus-like formations embedded in a fibrous connective tissue stroma widely infiltrated by fibroblasts and lymphocytes with occasional histiocytes. Ocular 10, objective 10.

Fig. 3 (case 1, from the nodule in the kidney).—Sinus-like spaces lined by endothelial cells in one or more rows, embedded in a fibrocellular connective tissue stroma rich in reticulum cells. Large deposits of blood pigment are present (upper right). Ocular 10, objective 10.

Fig. 4 (case 2, from the mediastinal tumor mass).—Sheaths of reticulum cells embedded in a thick network of argentaffin fibers, in the meshes of which sinus-like spaces are being formed. Ocular 10, objective 40.

well circumscribed and not tender. The tonsils and the tonsillar pillars were edematous and covered with grayish membranes. The cervical and submaxillary lymph nodes were palpable, and the spleen was moderately enlarged.

Repeated examinations of the blood from September 19 to 24 revealed a leukemic picture, with the white cell count ranging from 61,000 to 87,600, and marked anemia of a secondary type. The leukemic cell type was an immature cell with a loose chromatin network, one to three nucleoli, and a large round or bean-shaped nucleus surrounded by abundant basophilic cytoplasm in which azurophil granules could be seen at times. The impression was of a monocytic type of leukemia, and this seemed to be supported by the complete absence from the hemogram of transitional forms, either along the lines of the myeloid cell series or along the lines of the lymphoid cell series.

Roentgen examination showed, besides enlargement of the spleen, a sharply outlined mass extending upward from the lung root to the midportion of the left lung. The nature of this mass could not be determined definitely, but in view of the enlargement of the spleen and of the hematologic findings, it was thought to be a lymphoma.

The condition of the patient rapidly became worse, with repeated vomiting of large amounts of dark brown liquid material and with development of new tender ecchymotic areas on both arms and legs. Six days after admission the patient died.

Necropsy.—The body was that of a well developed, somewhat obese white woman with petechial hemorrhages disseminated throughout the body, most numerous at the upper and lower limbs. Moderate pitting edema was present at both ankles and at the dorsal region of the feet. The spleen and the liver could be palpated, and they appeared to be markedly enlarged. There was general lymphadenopathy of slight degree, most apparent at the neck and at the axillary and inguinal regions.

There were no adhesions or fluid in the abdominal cavity. The spleen was enlarged and moderately firm in consistency, and it weighed 350 Gm. The liver also was enlarged and extended 3 inches (7.5 cm.) below the costal margin at the level of the xiphoid process. It weighed 2,000 Gm., and both externally and on the cut section it displayed streaks of pale gray which stood out from the yellowish brown color of the hepatic parenchyma. The kidneys weighed 300 Gm. together and were not unusual externally, but when cut through they showed the limits between cortex and medulla to be indistinct, owing to a rather homogeneous grayish pink color throughout. None of the other abdominal organs showed significant changes.

When the thoracic cavity was opened, a large mass was seen to occupy most of the anterior mediastinum and to cover the upper third of the cardiac region. This mass, round in shape and 5 inches (12.5 cm.) in diameter, was loosely attached to the inner margin of the right lung; it was firm in consistency and slightly lobulated, and both externally and on the cut sections had a markedly variegated appearance owing to alternating grayish pink and spongy reddish brown areas.

The lungs and the heart were essentially normal except for patchy atherosclerotic changes in the coronary vascular tree.

Microscopic Observations.—Representative sections of the principal organs of the body when studied histologically made us modify our impression of the nature of the leukemic process. The liver, the spleen, the myocardium, the kidneys and the lymph nodes were found to be extensively infiltrated by leukemic cells. Quite

a number of these cells were young, immature blood cells, but all progressive stages of differentiation along the lines of myeloid cells could be recognized. Large cells, mononucleated or multinucleated, with characteristics of megakaryocytes were recognizable in the leukemic infiltrates, most numerous in the spleen and the lymph nodes. The myelogenous type of the leukemic process was further shown by the smears from the bone marrow, which displayed a predominance of myeloblasts and myelocytes.

The microscopic sections from the mediastinal tumor mass unexpectedly revealed it to be independent of the leukemic process. A loose interlacing of connective tissue fibers, in the meshes of which lay numerous blood capillaries and young mesenchymal cells, was the main feature of the growth. In some areas the vascular structure prevailed, while in some others the proliferation of mesenchymal cells was predominant (fig. 4). The majority of the blood vessels appeared as sinus-like spaces lined by a regular row of flattened endothelial cells, while elsewhere they showed a more evolved structure, as revealed by a distinct fibrous membrane in which muscular fibers could be recognized. Swelling of the lining endothelial cells and at times actual endothelial cell proliferation could be noticed in places, resulting in cellular processes protruding into the sinus spaces. Sheaths of cells identical in character could be recognized in the surrounding fibrous connective tissue stroma. A linear fissure or a larger opening was at times noticeable in the thickness of these cellular sheaths, and red blood cells well separated one from the other could be recognized in what appeared to be the earliest attempt at canalization of these newly formed endothelial buds. These sheaths of endothelial cells were embedded in a thick network of argentaffin fibers which spread throughout in spider-like fashion.

Dilatation and engorgement of the newly formed blood vessels often resulted in a cavernous-like tissue, and it was mainly in these areas that extravasated red blood cells and extracellular and intracellular blood pigment could be demonstrated.

Among the cells in the cellular portion of the growth, three different types were recognized. One type was an elongated, spindle-shaped cell with a large pale-stained vesicular nucleus, identified as a fibroblast. Another was a large round or polyhedral cell with thick short cytoplasmic processes which showed a tendency to fuse with similar processes of identical adjacent cells or with the pericellular argentaffin reticulum. Its nucleus showed a fine chromatin network, one or two nucleoli and a distinct nuclear membrane which was surrounded by abundant compact and basophilic cytoplasm. Its characteristics were those of a reticulum cell. While these two cell types were irregularly distributed and mixed, the third cell type showed a tendency to nodular arrangement, in groups of 20 to 30 cells or more. Under the low powers these cells resembled lymphocytes, but under the higher powers they were found to include plasma cells and quite numerous hematic blast cells with all transitional stages in the myeloid cell series. The possibility that these cells entered the tumor from the hematic stream could not be ruled out; however, in favor of their local origin were their frequent independence of the walls of the blood vessels and their localization in relatively avascular areas.

Summary.—In a woman aged 65 who died of myelogenous leukemia, postmortem examination revealed a mediastinal mass composed mainly of endothelial-lined sinuses and of impervious or canalized endothelial sprouts. These structures were embedded in a fibrocellular stroma

which displayed widespread proliferation of reticulum cells and fibers, fibroblasts and immature hematic cells. There were concomitant red blood cell extravasations, and blood pigment could be noticed in places.

CASE 3.—A 17 year old white American-born boy was admitted to the Framingham Union Hospital Dec. 25, 1945. He complained mainly of an ache in his left leg which radiated down below the knee. This pain was described as a steady ache which persisted even while he was lying perfectly still in bed. Two weeks before he had had similar pains in his right shoulder, but they were immediately relieved by lamp treatment.

Examination at admission encountered essentially normal conditions, and the diagnosis was "neuritis of the sciatic nerve." On January 12 an enlarged lymph node was noticed in the left supraclavicular fossa. It increased steadily in size during the following days, in spite of intensive penicillin treatment. No nodes were palpable elsewhere in the body, and the spleen and the liver were not enlarged. Repeated hematologic studies failed to reveal any significant deviation from the normal. The white blood cell count ranged between 6,000 and 8,300, with a hemogram within normal limits. The hemoglobin ranged between 17.5 and 14.5 Gm., and the red blood cell count between 5,000,000 and 4,100,000. The Hinton test was negative, as were the heterophilic antibody reaction and the Widal reaction for typhoid and paratyphoid. Blood chlorides amounted to 374 mg. per hundred cubic centimeters; serum amylase, 16 units (normal 16 to 64 units). The urine and the spinal fluid were essentially normal. Repeated determinations of the sedimentation rate showed it to be consistently accelerated. Roentgen studies failed to reveal any significant change except for fusion of the spinal processes of the first sacral segment with narrowing of the disks.

January 15 the supraclavicular lymph node was removed for histologic study. The specimen consisted of a firm bean-shaped formation which measured 3 by 1.5 by 1 inches (7.5 by 4 by 2.5 cm.). It was smooth, grayish pink and glistening externally, while on the cut section it showed a slightly lobulated appearance and a variegated color due to alternating pale gray and yellowish areas. On the microscopic sections the usual lymph-glandular structure was almost completely obliterated and replaced by a widespread proliferation of large polyhedral pale-stained cells with abundant basophilic cytoplasm and vesicular nuclei, rich in chromatin. Cells with two nuclei and occasional mitotic figures were present (fig. 5). These cells were enmeshed in a delicate reticulum of argentaffin fibers, more abundant around the walls of the lymph sinuses. From the fusion of these cells, large cellular sheaths were being formed. Fibroblasts were noticeable here and there, and granulocytic cells, either sparse or in small groups, were also present. The lymph sinuses were dilated and lined by swollen endothelial cells, many of which lay free in the lumens. The capsule of the lymph node was somewhat swollen and edematous but did not show evidence of cellular infiltration. Smears and cultures of the lymph node failed to reveal pathogenic micro-organisms. The pathologic diagnosis was a reticulum cell growth, aggressive in character.

Five days after the removal of the lymph node, pains developed in the upper part of the abdomen, more marked on the right. The entire abdomen was tender; there was a good deal of voluntary spasm, but at no time was involuntary spasm elicited. The abdomen was moderately distended, but no masses could be felt. The patient started to vomit frequently and looked severely ill. An exploratory laparotomy was considered, but in view of the development of a pericardial friction rub the operation was postponed. The condition of the patient became worse, and he died January 26.

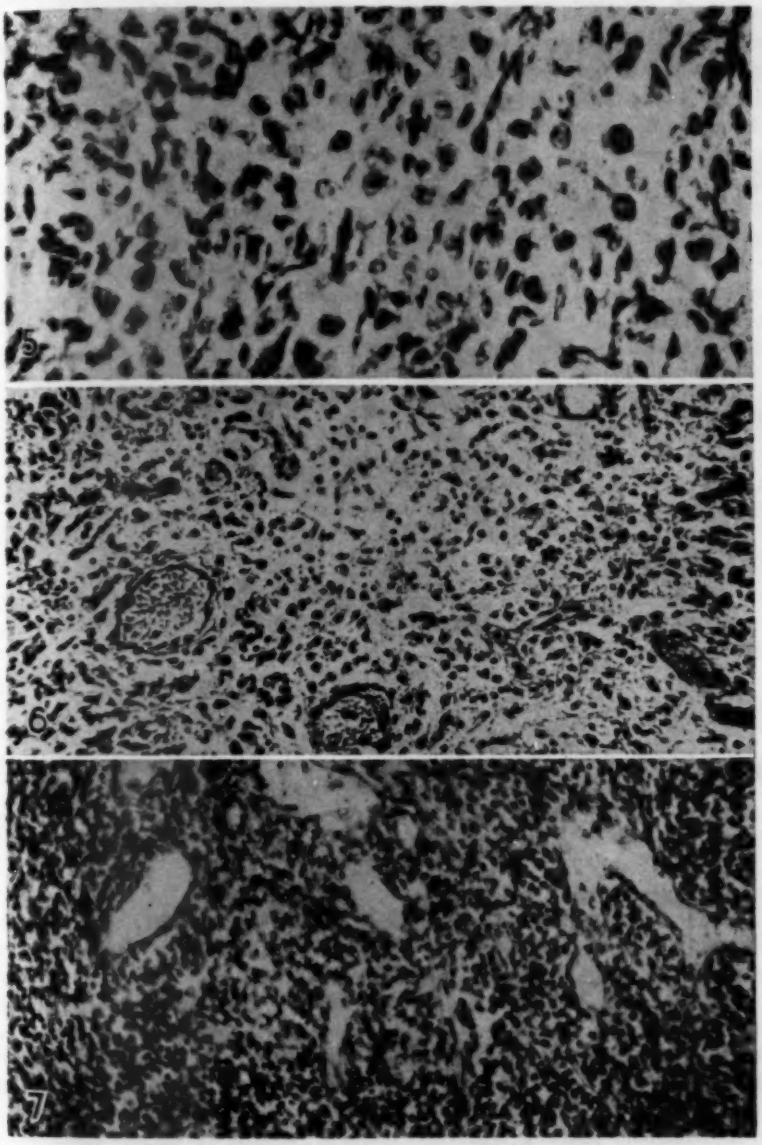

Fig. 5 (case 3, from the supraclavicular lymph node removed at biopsy).—Widespread proliferation of large, polyhedral, pale-stained reticulum cells with abundant basophilic cytoplasm and vesicular nuclei rich in chromatin. Cells with two nuclei and occasional mitotic figures are present. Ocular 10, objective 40.

Fig. 6 (case 3, from the intestinal nodule).—Thin-walled capillaries embedded in a fibrocellular stroma rich in large reticulum cells. Ocular 10, objective 10.

Fig. 7 (case 3, from the nodule in the liver).—Closely packed reticulum cells, irregularly mixed with lymphocytes and fibroblasts, embedded in which sinus-like formations containing red blood cells can be recognized. Ocular 10, objective 10.

Necropsy.—The body was that of a well developed but poorly nourished young man who appeared to be somewhat older than the stated age of 17 years. No injury or lesions of any type were noticeable in any part of the body except a slight pitting edema at both ankles. When the body was opened no significant changes were found in the organs of the chest. The lungs were free from adhesions and well aerated throughout; the heart was not unusual in shape and weighed 320 Gm. The parietal endocardium of the left auricle showed patchy fibrous thickening, and the mitral leaflets were moderately swollen and edematous, with small fibrous plaques at the free borders. The great omentum was retracted and both large and small intestines were distended by gas. There was no fluid in the peritoneal cavity, but both the parietal and the visceral peritoneum were congested throughout and slightly dull in appearance. A segment of ileum, 4 feet (about 1 meter) above the ileocecal valve, was coated by a thin layer of yellowish, easily detachable fibrinous material. On further examination of this segment of intestine, a portion of ileum was found to be invaginated into another portion of ileum. The intussusceptum measured 10 inches (25 cm.) in length. Both externally and on the mucosal side, the invaginated portion displayed extensive gangrenous hemorrhagic changes. A moderately firm nodule, 0.5 inch in diameter, grayish pink in color and spongy in appearance, bulged beneath the mucosa. Its gross appearance was not that of a polyp, and evaluation of its nature was left to the microscopic examination. The intussuscipiens surrounded the intussusceptum tightly, and was markedly congested and coated with a fibrinous exudate.

A nodule somewhat larger than that found in the intussuscepted intestinal loop, 3.4 inches (8.5 cm.) in diameter, but identical in character, was present in the liver. The latter was a rather large organ, not unusual in shape, which weighed 1,600 Gm. The grayish pink color of the nodule, which was embedded in the posterior border of the right lobe, contrasted sharply with the yellowish brown color of the surrounding hepatic parenchyma. The spleen also was moderately enlarged and weighed 250 Gm. It was firm in consistency and showed pulp increased in amount. Examination of the inguinal and axillary regions revealed an enlarged lymph node in the left axilla. It was the size of a bean, somewhat firm in consistency and homogeneously yellowish gray both externally and on the cut section. A few enlarged lymph nodes, similar in character, were found at dissection of the mesentery.

Microscopic Observations.—The microscopic study was centered in the nodule found in the intussuscepted portion of the intestine and in the hepatic nodule. The outstanding feature in both was an irregular network pattern resulting from the interlacing of connective tissue fibers, which were thick in some areas and thin in others, merging into broad bands of amorphous, amphophilic, nonfibrillar tissue. Elsewhere this network pattern was not so distinctly recognizable, owing to a dense infiltrate of cells which, although they showed great variations in size and shape, displayed a quite uniform intimate structure. The nuclei were large, round or oval, with a pronounced vesicular appearance. The chromatin was mostly condensed at the periphery of the nucleus, forming a distinct nuclear membrane. There were cells with several large nucleoli, and often two nuclei were seen. The surrounding cytoplasm was homogeneous, dark and compact in some cells, palely stained and finely vacuolated in some others owing to the presence of small fat droplets (sudan). Short cytoplasmic processes departed from the cell periphery to fuse either with similar processes of adjacent cells or with the network of collagenous and precollagenous fibers (Foot method) on which they rested. In other areas no intercellular material could be seen, and the cells of the growth appeared closely

packed, with loss of cellular outlines and a tendency to fuse together in large cellular sheaths. Sinus-like formation containing red blood cells or thin-walled capillaries were at times noticeable in the thickness of these compact cellular areas (fig. 6, from the intestinal nodule). Some of these vascular spaces seemed to lie in direct contact with the elements of the cellular bed in which they lay without the interposition of any other cellular type or fibrillar structure (fig. 7, from the nodule in the liver). Some others showed a more or less regular lining of flattened or spindle-shaped cells, whose elongated vesicular nuclei contrasted sharply with the dark-stained round nuclei of the surrounding cells. The cellular elements lining these spaces were disposed at times in a discontinuous single-layered row; at other times they showed overlapping, giving rise to cellular spurs protruding into the sinus spaces. Large hemorrhages and deposits of blood pigment, either free or in macrophages, were present.

In both the hepatic and the intestinal localization the tissue new growth was accompanied by extensive damage of the local structures. There was complete obliteration of hepatic cells in some areas, while in some other areas the hepatic cords appeared spread apart or atrophied with loss of any trace of acinous arrangement. The same was true of the nodule in the intestine, where, in addition, the tumor picture appeared overshadowed at many points by tissue necrobiosis and by infiltration of the tissue by inflammatory cells in concomitance with the intestinal intussusception.

Changes identical with those characterizing the hepatic and the intestinal nodule could be recognized not only in proximity to, but also at a certain distance from, the nodules themselves. As neither the lymphatic nor the hematic blood channels showed evidence of invasion by tumor structures, the impression was that these extranodular lesions were not metastatic but independently originated.

Among the changes in the other organs, those encountered in the spleen and in some axillary and mesenteric lymph nodes are worth mentioning. In the spleen the limits between pulp and follicles were rather poorly preserved. This was mostly due to a diffuse hyperplasia of reticulum cells, equally affecting the lymph follicles and the pulp in broad areas. In the lymph follicles the hyperplasia of reticulum cells involved the central portion most conspicuously. This appeared to be replaced by pale-stained large cells, round or oval, with short and drawn-out acidophil cytoplasmic processes. Their nuclei were oval, with unfolded nuclear membranes and a scanty fine chromatin network containing small nucleoli at times. Two nuclei were often present. Cells identical in type were seen in the pulp. The arrangement of the cells varied greatly. There were areas in which the cells lay in close proximity, with scanty intercellular material. Elsewhere the cells lay in nests, forming an alveolar or mosaic arrangement which gave the appearance of an epithelial growth. In other places they were disposed in rows, with a tendency to form intersecting trabeculae. The histologic resemblance of these cells to the cells lining the sinuses appeared unquestionable, and the finding was interpreted as early attempts at sinus formation. The sinuses were engorged and showed swelling and at times actual proliferation of the endothelial linings, accompanied by abundant cellular desquamation. Extensive extravasations of red blood cells were noticeable in places. Some were recent and others old, with large deposits of blood pigment either free or contained in large histiocytic macrophages.

A fundamentally identical structure was shown by the axillary and mesenteric lymph nodes, many of which displayed hyperplasia of reticulum cells in broad areas with reduction of lymphocytes. Cells with two nuclei and occasional mitotic

figures could be recognized among the proliferated reticulum cells, which displayed a marked tendency to syncytial arrangement. The lymph sinuses were dilated and showed pronounced swelling and desquamation of the endothelial linings.

Summary.—In a boy aged 17 years who died of intestinal intussusception postmortem examination revealed a bluish red spongy submucous nodule in the intussuscepted portion of the intestine. A similar nodule was present in the liver. Both were found to be composed of sinus-like spaces and thin-walled blood capillaries embedded in a cellular stroma mostly composed of reticulum cells and fibers. Large hemorrhages and deposits of blood pigment were present. Changes identical with those characterizing the intestinal and hepatic nodules were noticeable in proximity to, and at a certain distance from, the nodules themselves, and were interpreted as being independently originated. There was concomitant enlargement of the spleen and of the lymph nodes, which showed a striking proliferation of reticulum cells with patterns suggesting early attempts at sinus formation.

COMMENT

The subdivision of vascular growths into nonneoplastic, noncancerous neoplastic, and cancerous is generally accepted (Aegerter and Peale [9]). To the first group belong varicosity, telangectasia, cirsoid aneurysm, phlebarteriectasia, diffuse phlebectasia of the limbs and congenital arteriovenous fistula, all characterized by a malformative process consisting either in faulty distribution or in faulty development of the blood vessels in a circumscribed area of the body.

A quantitative and, to a certain extent, qualitative disorder of vascularity is characteristic of the group of noncancerous neoplastic growths, exemplified by angioma simplex and by angioma hypertrophicus of Zigler, capillary or cavernous, all of which are based on a benign new formation of vascular structures.

Anaplastic and disorderly proliferation of blood vessels, accompanied by a more or less aggressive new formation either of periadventitial connective tissue cells (angiosarcoma) or of endothelial cells lining the intima (angioendothelioma, capillary endothelioma), is the feature of the cancerous growths.

Although it is provided with a lower grade of malignancy, hemoangioblastoma has recently been added to the group of cancerous growths. It is characterized by the presence of pseudo-xanthomatous cells embedded in the meshes of a reticulum of argentaffin fibers in the interstices of the newly formed blood vessels. "Solid hemoangioblastoma" is the term given to the growths in which cellular proliferation prevails; the growths in which vascular proliferation, under various forms, is predominant are called cystic capillary or cavernomatous hemangioblastoma.

This being the accepted scheme of classification, there are a number of cases of vascular growth reported in the literature which, although belonging to the group, hardly fit in any of the categories. This is true for our cases, in which new formation of blood channels in all localizations was the most striking but not the only feature. They showed proliferation of endothelial and adventitial connective tissue cells, phagocytic histiocytes, fibroblasts, lymphoid elements, a well organized reticulum and in 1 case immature hematic cells, as well.

In the past, one gathers, such growths have been classified among the hemangioendotheliomas, on the assumption that only the prolific vascular endothelium could give rise to such structures. Considering that the vascular endothelial cell is nothing more than a functional adaptation of the pluripotent periadventitial cell, we feel that this cell and not the product of its differentiation must be considered as the basic cellular unit involved in the process. For the same reason we do not agree with the conception of Orsós [38] who, in describing a number of vascular tumors, some composed partly of blood capillaries and partly of endothelial sprouts, and some much more complex, with both capillaries and immature hematic cells, concluded that blood vessels and blood cells had originated from an embryonal angioblastic cell. The term "angioblast" proposed by Orsós implicitly limits the developmental possibilities of this embryonal cell, which in our opinion has much broader evolutive possibilities. The old conception of Albrecht of a developmental defect underlying a number of vascular growths has been stressed more recently by several authors. An inclusion of angioblastic structures occurring in the central nervous system is advocated by Roussy and Oberling [39] to explain the development of certain vascular tumors of the brain. The disembryoblastic origin of Lindau's disease is apparent, and the fact that it is not infrequently accompanied by other organic malformative processes had made some consider the possibility of a more general developmental defect (Tedeschi [40]).

In a case of cavernous degeneration of the liver that one of us had the opportunity of studying (Tedeschi), the vascular defect extended beyond the cavernous area and the whole vascular structure of the liver appeared to be disarranged; in another case of angiomatosis of the liver observed by the same author, the disembryoblastic nature of the process was emphasized by a peculiar syncytial arrangement of the hepatic cells, by the apparent absence of any endothelial lining in many of the sinusoidal spaces and by the paucity and irregularity of distribution of the reticulum of argentaffin fibers. A case somewhat similar

38. Orsós, F.: Beitr. z. path. Anat. u. z. allg. Path. **93**:121, 1934.

39. Cited by Tedeschi.[40]

40. Tedeschi, C. G.: Riv. sper. di freniat. **56**:497, 1932.

to this was described by Lunghetti,[39] that of a telangiectatic liver in which structural changes were clearly noticeable in both arteries and veins beyond the telangiectatic areas.

In describing a familial telangiectatic dysplasia of the Osler type, Weber [41] alluded to the possible analogy and association of the telangiectatic condition of the skin and mucous membranes of the nose and the mouth with certain hemorrhagic telangiectatic conditions of the stomach, the intestines, the kidneys or the lungs. The telangiectasia in this disease he regarded as due to a congenital developmental dysplasia of the small vessels, potentially present at birth though often not manifesting itself till after puberty.

The possibility that a malignant vascular growth originates from a localized debility in the vascular system is shown by a number of cases in the literature. In the hemolymphangiosarcoma of the liver described by Pepere [39] the hepatic capillary network obviously showed deviations from the normal in areas situated far beyond the new growth. In a similar observation by Mark [39] a hemoangiosarcoma of the liver appeared to have originated from a preexisting cavernous angioma. The same was thought to be true of a cavernoma of the spleen described by Wright,[39] which showed proliferation both of lining endothelial cells and of interstitial mesenchymal cells; an identical structure was shown by a hepatic nodule that was considered to be metastatic. In discussing an unusual tumor of the liver, characterized by multiple nodules composed of blood capillaries, endothelial cells in atypical proliferation, giant cells and foci of extramedullary hemopoiesis, Fisher [39] concluded that the growth had originated in a faulty development of the capillary bed of the organ.

A similar interpretation might be offered for our cases, for which it is logical to suppose that the growths started independently on the ground of a focal vascular debility, congenital or acquired. However, considering the number of structures involved in the growth, we should locate this debility not in the vascular system but in the mesenchymal syncytium, the only system in the body which under the influence of adequite stimuli is potentially able to differentiate itself into the many lines of development shown by the growths in the different localizations.

Histologic evidence to support this belief was found in what appeared to be transitional forms from reticulum cells and the flat endothelial cell forerunners of the vascular channels, in the demonstration of fine processes interpreted as early attempts at formation of the fibrillar reticulum noticed on the surface of the cytoplasmic reticulum, and in the formation of hematic cells (case 3) which seemed to be initiated by a basophilia developing in the perinuclear zone of the cytoplasmic syncytium. Simultaneously, the nucleus showed coarser chromatin

41. Weber, F. P.: Brit. J. Dermat. **48**:182, 1936.

granules, and the nucleoli became more conspicuous, the result being the formation of a cell with the cytoplasmic and nuclear characteristics of a hemocytoblast. Some of these cells still possessed stellate processes, but others became gradually rounded off and through progressive stages they assumed the characteristics of myeloblasts and myelocytes.

Foci of hemopoiesis in vascular tumors have been reported in a number of cases. In that of Fisher,[39] immature hematic cells could be recognized in hepatic nodules composed of sheaths of endothelial cells and of blood channels resting in a fibrous connective tissue stroma, embedded in which were young mesenchymal cells, scattered throughout. A tumor in the liver described by Pilliet and Schmieden [39] and one of the dura mater described by Albrecht [39] showed similar structures. Under the title *kombinierte Formen* Roulet [42] described reticulum cell tumors of different organs, in which either leukemic or lymphogranuloma-like features were concomitant findings. Similar observations in lymph-glandular structures were reported by Vecchi [43] and by Montpellier, Manceaux and Assan,[44] all authors agreeing in the belief that there was an atypical growth evolving in more than one direction from an undifferentiated stem cell. Accordingly, Oberling [45] and later Craciun and Ursu [46] have recognized in the broad group of reticulum cell tumors myelogenous reticulomas and lymphogenous reticulomas, characterized by striking differentiation of the pluripotent parent reticulum cell into myelogenous or lymphatic cells.

The question arises whether the nodular lesions found in various organs in our 3 cases can be identified from the histologic standpoint with the cutaneous nodular manifestations of Kaposi's disease. After close comparison between the findings in our cases, the findings reported by other students and personal observations on biopsy material from cutaneous nodules, our impression is that the patterns of the visceral nodules in our cases exactly overlap the patterns of the cutaneous nodules in Kaposi's disease. Choisser and Ramsey,[2] in discussing their cardiac new growths, arrived at a similar conclusion; however, in view of the absence of cutaneous lesions they felt that the morphologic diagnosis of angioreticuloendothelioma was better than that of Kaposi's disease. We felt the same at the time when cases 1 and 2 were being investigated, but on further study of these 2 cases and the third similar case, having reached the conviction that the visceral lesions in our cases were identical with those of cutaneous Kaposi's disease, we no

42. Roulet, F.: Virchows Arch. f. path. Anat. **277**:15, 1930; **286**:702, 1932.
43. Vecchi, G.: Cancro **5**:45, 1934.
44. Montpellier, J.; Manceaux, A., and Assan: Gaz. méd. de France, 1931, p. 667.
45. Oberling, C.: Bull. Assoc. franç. p. l'étude du cancer **17**:259, 1928.
46. Craciun, E. C., and Ursu, A.: Bull. Assoc. franç. p. l'étude du cancer **22**:711. 1933.

longer see why, in a systemic process likely to involve any part of the body and to affect independently, simultaneously or successively both skin and internal organs, all manifestations, whatsoever their localization, should not be covered by the same label. Eponyms, it is true, are not often desirable, yet they might be in regard to a disease process such as the one under consideration, characterized by a great variety of histologic patterns which are inherent to the multiple developmental potentialities of the basic unit of growth, the reticulum cell.

The dispute over the hyperplastic or dysplastic nature of Kaposi's disease, which has been carried on since the early description of the process, is, in our opinion, futile. Both hyperplastic and dysplastic growths can be expected. A hyperplastic type of growth, corresponding to the inflammatory or granulomatous stage of MacKee and Cipollaro's classification,[18] will occur whenever the differentiation of the unit of growth into various cell types proceeds harmoniously along the lines of normal development, with fairly well balanced proliferation of vascular elements and supporting fibrocellular stroma; on loss of this organizing power a dysplastic type of growth will occur, provided with wild and aggressive potentialities, and if the vegetative function of the cell type involved in the process prevails, it will result in a solid cellular tumor, hardly distinguishable from a sarcomatous growth.

There are a number of visceral growths reported in the literature which simulate closely those observed in our cases. The splenic hemangiosarcoma most recently described by Bauer and Stanford,[47] mainly composed of blood-filled channels lined by a stratified layer of cells, of a thick network of reticulum fibers and of a cell type which in some places simulated fibroblasts, elsewhere macrophages, and in still other places endothelial cells lining the normal splenic sinuses, exemplifies many similar pleomorphic vascular growths recorded in the literature under a number of names. In keeping with the fundamental structure of Kaposi's disease these growths might be explained on the basis of a differentiation along various lines of the pluripotent reticulum cell. The tonsils, the bones, the vertebral bodies and the liver were involved by an identical process in the case of Bauer and Stanford.[47] This was interpreted as metastatic, and it may have been metastatic, but it cannot be disproved that there may have been an autonomous origin underlying a systemic involvement of the reticuloendothelial system. This explanation might apply also to the so-called metastasizing hemangioma (Robinson and Castleman[48]; Ward and Jones[49]) and to the angioblastic or hypertrophic type of hemangioma,

47. Bauer, D. F., and Stanford, W. B.: Arch. Path. **41**:668, 1946.
48. Robinson, J. M., and Castleman, B.: Ann. Surg. **104**:453, 1936.
49. Ward, G. E., and Jones, A. F.: Ann. Surg. **36**:330, 1938.

often mistaken microscopically for hemangiosarcoma and as a matter of fact frequently observed to be locally aggressive and prone to recur after operation (Watson and McCarthy [50]). A good number of these growths might fit, in our opinion, in a broader conception of Kaposi's disease, namely that of a systemic process of the reticuloendothelial system likely to involve independently and in an unpredictable manner, simultaneously or successively, the skin and the internal organs and characterized from the histologic standpoint by a great variety of patterns which are inherent to the multiple developmental potentialities of the basic unit of growth, the reticulum cell.

SUMMARY

The literature on Kaposi's disease is reviewed and analyzed with special reference to the visceral manifestations. From the study of 2 cases in which the liver, the kidney and the small bowel showed multiple independent growths and of a third case with mediastinal localization, all the growths consisting of newly formed blood channels and including proliferations of endothelial and adventitial connective tissue cells, of phagocytic histiocytes, of fibroblasts, of lymphoid elements, of a well organized reticulum and, in one case, of immature hematic cells, the conclusion is reached that the patterns of the visceral lesions in these cases were identical with those of the cutaneous lesions of Kaposi's disease. The conception is advanced that Kaposi's disease is systemic in nature and likely to involve independently and in an unpredictable manner, simultaneously or successively, the skin and the internal organs and that it is characterized from the histologic standpoint by a great variety of patterns inherent to the multiple developmental potentialities of the basic unit of growth, the reticulum cell.

50. Watson, W. L., and McCarthy, W. C.: Surg., Gynec. & Obst. **71**:569, 1940.

FIBROSARCOMA OF THE EPIDIDYMIS

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NEOPLASMS originating in the epididymis are rare.[1] According to Charache,[2] 22 benign and 54 cancerous neoplasms of the epididymis were recorded up to 1939. Charache combined the cases collected by Scalfi [3] with those tabulated by Lazarus.[4] Among all these 1 was listed as an instance of spindle cell sarcoma and 1 as an instance of fibrosarcoma. The fibrosarcoma, described by Lazarus, occurred in a patient 44 years old. The only one reported since is that described by O'Brien,[5] in a patient 20 years old. The case herein presented is believed to be the third recorded instance of a fibrosarcoma of the epididymis and the first of fibrosarcoma occurring in early childhood.

REPORT OF A CASE

A 3 year old white boy was admitted to the University of Oklahoma Hospitals, Sept. 18, 1945, with a mass in the right side of the scrotum, first noticed in June 1945. The mass enlarged rapidly and became painful a few days before admission. There were no other genitourinary symptoms. The child was well developed and well nourished. Except for the enlargement of the scrotum, no abnormalities were noted. The left testicle was of usual size, and the testis and epididymis could be felt. The content of the right side of the scrotum was replaced by a firm, smooth, slightly tender mass, 7 by 5 cm., with the epididymis not palpable. There was no increase of local heat. The mass could not be transilluminated.

Urinalysis gave essentially negative results. The red blood cell count was 4,750,000; the hemoglobin content was 13 Gm.; the white blood cell count was 5,500, with polymorphonuclears 55, lymphocytes 35, eosinophils 5 and monocytes 5 per cent. The Mazzini test of the blood was negative. On September 22 the content of the right side of the scrotum including the spermatic cord up to the level of the external inguinal ring was removed (by Dr. Herman F. Flanigin).

From the Department of Pathology, University of Oklahoma School of Medicine.

1. Halpert, B.: J. Urol. **45**:536, 1941. Golden, A., and Ash, J. E.: Am. J. Path. **21**:63, 1945. Sworn, B. R.; Marshall, F. W., and Edwards, J. L.: Brit. J. Surg. **33**:375, 1946.

2. Charache, H.: Urol. & Cutan. Rev. **43**:663, 1939.

3. Scalfi, A.: Ann. ital. di chir. **15**:81, 1936.

4. Lazarus, J. A.: J. Urol. **39**:750, 1938.

5. O'Brien, M. G.: J. Urol. **47**:311, 1942.

The specimen consisted of an oval mass, 8 by 5 by 4 cm., weighing 100 Gm. The external surface was smooth and gray-white. On the cut surfaces there was a gray-white fibrillar, finely striated pattern with no areas of discoloration or hemorrhage. A horseshoe-shaped slitlike space, corresponding to the cavity of the tunica vaginalis propria, surrounded a smooth oval nodule, 2 cm. long, which was continuous at its base, 1 cm. wide, with the rest of the growth (fig. 1).

Microscopic sections taken from various parts of the mass and from the nodule and stained with hematoxylin and eosin disclosed that the mass was the epididymis and the nodule the testis. In the latter the primordial seminiferous tubules were of proportionate size and of usual distribution within the usual amount of fibrous connective tissue. The testis was bordered by the intact tunica albuginea. In the mass, spread apart by neoplastic fibrous connective tissue, were the tubules

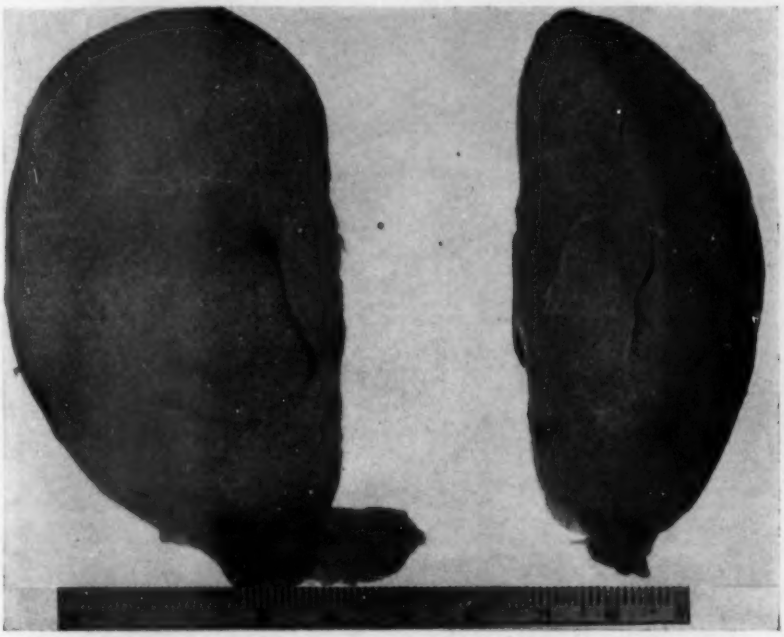

Fig. 1.—Cut surfaces of the scrotal mass. The horseshoe-shaped slitlike space corresponds to the cavity of the tunica vaginalis propria. The nodule is the testis, and the mass is the epididymis.

of the epididymis, lined by tall columnar epithelium (fig. 2*A*). The neoplastic tissue had a delicate fibrillar pattern with various sized, round or elongated, deeply stained nuclei in a streamlike arrangement. The elongated nuclei were blunt or pointed at their ends. Some cells were seen in a state of division. The cytoplasmic borders were not discernible, and the cytoplasm faded into the fibrillar ground substance. The stream or whorl-like arrangement of the cell nuclei and fibrils was more marked in some fields than in others (fig. 2*B*). Delicate-walled blood vessels were scattered throughout. Minute areas of hemorrhage and necrosis were seen in places.

Roentgen radiation was given over a period of thirty days (October 3 to November 3) to three fields, one including the right inguinal area and the right

half of the scrotum, one located posteriorly over the lumbar region, and one over the sacral area (total dose, 1,800 roentgens to each field; distance, 50 cm.; 200 kilovolts; 18 milliamperes; Thoraeus filter).

On account of local reaction, radiation therapy was discontinued and the patient discharged on November 9. He was followed in the outpatient department until

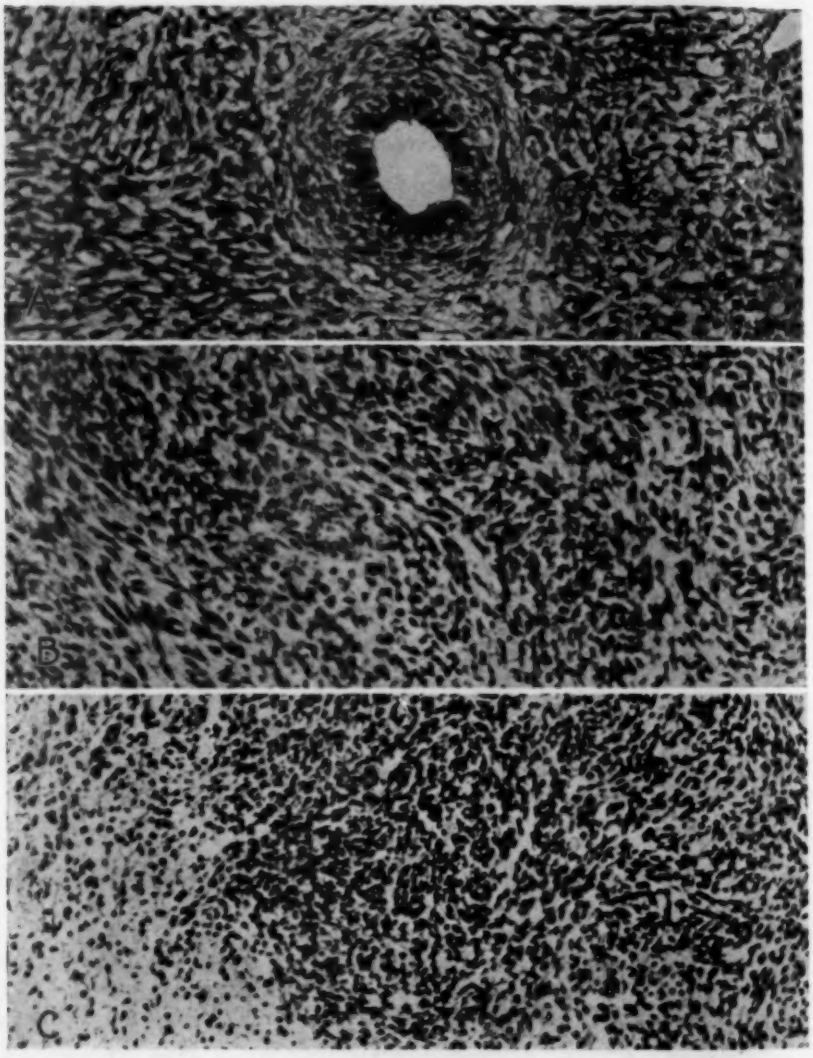

Fig. 2.—Fibrosarcoma of the epididymis. *A* shows a tubule of the epididymis lined by tall columnar cells and surrounded by neoplastic fibrous connective tissue. In *B* the neoplastic tissue is seen to have a delicate fibrillar pattern, with round or elongated, deeply stained nuclei in a streamlike arrangement. *C* reveals that the retroperitoneal mass has a microscopic appearance similar to that of the original growth. × 150.

July 8, 1946, when he was readmitted to the hospital. At this time the complaints were loss of appetite, weakness, constipation, fever and pain in the right side of the abdomen. The child was emaciated and appeared chronically ill. The temperature was 100 F., the pulse rate 88 and the respiratory rate 20. A healed scar marked the site of operation, and the right scrotum was empty. The left testicle was of usual size. In the right side of the abdomen a firm, slightly tender mass was felt, extending from the iliac crest to the costal margin and from the flank to the midclavicular line.

The urine was yellow, cloudy, with a p_H of 7.5; it revealed no albumin and no sugar. The red blood cell count was 3,470,000; the hemoglobin content was 8 Gm.; the white blood cell count was 10,650, with polymorphonuclears 73 (stab forms 4), lymphocytes 24, eosinophils 2 and monocytes 1 per cent. Intravenous urography on July 23 failed to visualize the pelvis of the right kidney; that of the left seemed as usual. Cystoscopic examination, July 27, disclosed no lesions in the urinary bladder. An attempt to pass a catheter through the right ureter was unsuccessful. The abdominal mass continued to enlarge, and the abdomen became distended with fluid. The temperature varied between 96 and 103 F.; the pulse rate, between 126 and 144. There was rapid loss of weight and strength. Supportive measures were of no avail, and the child died August 10.

Necropsy (eight hours after death).—The body was 100 cm. long and weighed approximately 30 pounds (13.5 Kg.). The face had a wizened appearance. The neck and the chest were symmetric. The skin was tightly drawn over the ribs. The abdomen was prominent and tense. There was a scar 3 cm. long to the right of the root of the penis. The content of the right scrotum was missing; the left testis was of usual size. There was marked wasting of the flesh of the upper and lower extremities, with the skeletal markings prominent.

The peritoneal cavity contained 750 cc. of light milky fluid. The greater omentum was gray-white and up to 2 cm. thick, and its free portion was adherent to the anterior abdominal wall and the fundus of the urinary bladder. The edge of the liver was 5 cm. above the costal margin in the right midclavicular line. The surface of the diaphragm was studded with neoplastic nodules up to 0.7 cm. in diameter which were elevated as much as 0.4 cm. The surfaces of the small intestine and the mesentery were glazed by a thin coating of apparently neoplastic tissue. A retroperitoneal mass, 17 by 13 cm., protruded from the posterior abdominal wall, pushing forward the overlying terminal portion of the ileum, the cecum with the appendix, and the ascending colon. It extended behind, and was adherent to, the right kidney without invading it. The mass was extremely friable and was composed of gray-white tissue mottled with yellow and red. It contained various-sized locules with ragged inner surfaces containing tissue debris, clotted blood and bloody fluid. The mass measured 14 by 10 by 8 cm. after removal and after most of its fluid content had been evacuated.

There was no neoplastic involvement of the pleural and pericardial surfaces. The left testis and epididymis measured 1.5 by 1 cm. and were of usual appearance externally and on their cut surfaces. There was no involvement of the prostate, the urinary bladder, the ureters, the renal pelves, the kidneys or the adrenal glands. The pancreas itself was uninvolved; likewise, the extrahepatic biliary ducts, the gallbladder, the liver and the spleen. There was no involvement of the lungs and of the tracheobronchial lymph nodes.

Microscopic preparations from the greater omentum and from various parts of the retroperitoneal mass disclosed a delicate fibrillar pattern and round or elongated, deeply stained nuclei in a streamlike arrangement similar to that seen in the

original preparation from the epididymis (fig. 2*C*). There were massive areas of necrosis with old and more recent hemorrhage. No epithelial elements were seen in any of the preparations. No neoplastic involvement was seen in preparations from the lungs, the spleen, the liver, the pancreas, the adrenal glands and the kidneys. The left testis and epididymis had the usual structure corresponding to the age of the patient, and there was no evidence of neoplastic involvement.

COMMENT

The microscopic structure of the original growth and its relation to the testicle leave no doubt that the neoplasm originated in the stroma of the epididymis. The epithelium-lined tubules seen in the original growth were those of the epididymis and were not neoplastic. In the extensions of the growth outside the epididymis there were no epithelial elements. The neoplasm resembled closely Wilms's tumor minus its epithelial elements and was probably derived from a similar anlage.

There was little change in the structural pattern of the growth except that areas of necrosis and hemorrhage became more extensive as the neoplasm increased in bulk. The involvement was by direct extension with no apparent spread by the lymphatics or by the blood stream. It is likely that at the time of removal of the right scrotal content, extension along the spermatic cord into the retroperitoneal tissues had already occurred. The short time, less than one year, which elapsed before the death of the patient indicates the rate of growth of the neoplasm. Had the neoplasm been removed earlier, extension might have been prevented.

SUMMARY

A fibrosarcoma of the right epididymis occurring in a 3 year old boy is reported. The child died of the neoplasm less than one year after surgical removal of the scrotal content. This is believed to be the third recorded instance of fibrosarcoma of the epididymis and the first of fibrosarcoma occurring in early childhood.

SOME MANIFESTATIONS OF VITAMIN E DEFICIENCY IN THE MONKEY

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ONE OR more of the recognized manifestations of vitamin E deficiency (fetal death and resorption, testicular degeneration, muscular dystrophy, accumulations of an inert pigment in the musculature and the reticuloendothelial system) have been observed in a considerable number of laboratory mammals. There appears, however, to be no recorded demonstration of this deficiency state as produced in the monkey. The lack of direct evidence concerning vitamin E deficiency of man emphasizes the need for some knowledge of the reactions of other primates to depletion of vitamin E. The present report records certain observations made on young monkeys maintained for several years on a diet deficient in vitamin E. Although the sexual immaturity of the animals used did not permit any investigation of reproductive functions, other gross and histologic observations, especially those relating to an acid-fast pigment that occurred in certain locations, resulted in findings quite similar to those previously reported for the rat [1] and observed also in other laboratory animals.[2] These observations are presented as evidence of a state of vitamin E deficiency induced in the Macaca rhesus monkey.

MATERIAL AND METHODS

In the course of planning a vitamin E–deficient diet sufficiently palatable for prolonged feeding of monkeys, it was suggested that rice might be utilized as a major constituent. In order to be assured of rice with a low content of the vitamin, several hundred grains from different lots (obtained on the local market

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An abstract of these studies was presented before the American Association of Anatomists (Anat. Rec. **94**:522, 1946).

These investigations have been aided by a grant made to one of us (Ira R. Telford) from the Milbank Memorial Fund.

From the departments of anatomy of the University of Rochester School of Medicine and Dentistry, Rochester, N. Y., and the George Washington University Medical School, Washington, D. C.

1. (*a*) Martin, A. J. P., and Moore, T.: J. Hyg. **39**:643, 1939. (*b*) Mason, K. E., and Emmel, A. F.: Anat. Rec. **92**:33, 1945.

2. Unpublished studies from this laboratory.

and directly from the millers) were examined with a dissecting microscope and the samples rated in terms of the percentage of grains still possessing the germ or fragments thereof.[3] Wide variations were found in the samples examined. When we assayed the lots by rearing newly weaned female rats on vitamin E–deficient diets in which rice from the different lots was fed at a 50 per cent level, those lots rating 10 to 20 per cent consistently produced no fertility responses; samples rating 60 per cent or higher permitted positive responses in some of the test animals. Consequently, rice lots rating 10 per cent or less were selected for purchase and used in the experimental diet. The latter was composed as follows: 500 Gm. of cooked rice, 300 Gm. of skimmed milk powder, 180 Gm. of dry brewers' yeast and 300 Gm. of a vitamin E–deficient diet used for rats (containing casein, 20 per cent; corn starch, 50 per cent; lard, 18 per cent; salts, 2.5 per cent; brewers' yeast, 7.5 per cent; cod liver oil, 2 per cent). The diet was made up twice weekly and stored at 6 to 10 C. until just before feeding, when 25 cc. of orange juice or 25 mg. of ascorbic acid was added to the portion fed each monkey.

Six sexually immature monkeys (3 males and 3 females), estimated to be 2 to 3 years of age and varying in weight from 2 to 2.5 Kg. in body weight, were placed on the experimental diet. One male and one female died after about five months; because of advanced postmortem changes, no tissues were preserved for histologic study. The remaining 4 animals grew well and maintained good health during the first two years of the experiment. Eventually, progressive weakness and gradual loss of appetite, extending over a period of three or four weeks, appeared in 2 animals after approximately twenty-five months and in the other 2 after about thirty-one months. All showed progressive inability to climb or cling to the walls of the cage enclosures. As weakness of the digital flexor muscles became apparent the animals could cling to the walls only by inserting the forearm through the coarse wire mesh; later they refused to climb, remaining relatively inactive on the floor of the cage. During these terminal stages they consumed but little of the experimental diet and would accept only small amounts of bread, milk or orange juice.

One male was found dead after seven hundred and seventy-two days, and 2 females after seven hundred and eighty and nine hundred and fifty-six days, of experimental feeding. An autopsy was made on each within four hours after death. The remaining male was killed on the nine hundred and sixty-sixth day of feeding. In all monkeys, the lymph nodes and the smooth musculature of the gastrointestinal tract showed variable degrees of brownish discoloration, the skeletal musculature appeared somewhat pale and lusterless, and there was considerable depletion of the various fat depots. Only the male that died after seven hundred and seventy-two days of feeding showed evidence of tuberculosis; the lesions were sufficiently extensive to have contributed to the early death of this animal. Except for the dystrophic state of the skeletal musculature, the gross and microscopic changes in the other experimental animals provided no adequate explanation for their decline or death.

Because of the limited number of young monkeys available at the time these studies were begun, and the somewhat exploratory nature of the investigation, no animals were fed the experimental diet supplemented with tocopherol. Instead, 2 male and 2 female monkeys maintained for a year or more on the mixed diet

3. Dr. C. P. Leblond, of the Department of Anatomy, McGill University Medical School, made these suggestions and gave other assistance in the preliminary phases of this study.

of the stock colony and approximately 5 years of age at autopsy provided control tissues for comparison. The methods of fixation, embedding and staining were the same as for the tissues of the experimental monkeys. With both groups histologic studies were carried out on all visceral organs and on lymph nodes and skeletal muscles from various regions.

Tissues were fixed in Zenker's solution with acetic acid (5 per cent), embedded in paraffin and sectioned at 5 to 7 microns. Sections were routinely stained with (1) hematoxylin and eosin and (2) Verhoeff's or Kinyoun's carbolfuchsin, then destained with acidified alcohol for fifteen to thirty minutes and subsequently stained with Ehrlich's hematoxylin. Staining with Kinyoun's carbolfuchsin (phenol crystals, 8 Gm.; basic fuchsin, 4 Gm.; 95 per cent alcohol, 20 cc.; water, 100 cc.) for one hour at room temperature gave the most satisfactory results. Various other staining procedures were used to permit further characterization of the acid-fast pigment.

EXPERIMENTAL DATA

The pigment referred to throughout this report appeared pale brown in hematoxylin-eosin preparations and varied from brick red to brilliant red after acid-fast staining. It showed moderate affinity for iron-hematoxylin, exhibited a yellowish or yellowish brown fluorescence when examined under the fluorescent microscope, gave a positive Feulgen reaction, and stained yellowish to orange with sudan IV and black with sudan black in paraffin sections (previously exposed to fat solvents). In these various respects it closely resembled the pigment previously described in vitamin E–deficient rats,[1] and since found to characterize vitamin E deficiency in the mouse, the hamster, the cotton rat and the dog.[2] The general pattern of distribution of this pigment, however, differs considerably in the various species mentioned.

Tissues of the control monkeys were devoid of pigment except for traces of acid-fast material in an occasional macrophage and in cells of the adrenal cortex. The skeletal muscles showed no dystrophic change, but in 2 animals there was considerable Sarcocystis infection, as briefly reported elsewhere.[4] There were no other pathologic changes of note.

One of the 4 monkeys fed the vitamin E–deficient diet showed moderately extensive tuberculous lesions of the respiratory and digestive tracts; otherwise, no significant pathologic developments were observed other than the dystrophic changes in skeletal muscles and the occurrence of acid-fast pigment at various sites as discussed in subsequent sections. While the pattern of the deposition of pigment was the same in all experimental monkeys, the amounts of pigment encountered in the various locations were somewhat greater in the 2 animals continued on experiment for nine hundred and fifty-six and nine hundred and sixty-six days than in the 2 that succumbed after seven hundred and seventy-two and seven hundred and eighty days, respectively.

4. Offutt, E. P., and Telford, I. R.: J. Parasitol. (supp.) **31**:15, 1945.

Skeletal Muscle.—The muscles studied were the diaphragm, the rectus abdominis, the pectoralis major, the psoas major, the adductor magnus and the gluteus maximus. All showed degenerative lesions, varying from slight fibrosis with some leukocytic infiltration to rather extensive atrophy and necrosis involving a considerable number of muscle fibers (fig. 1). Only occasionally were pigment granules demonstrable within the degenerating fibers and in macrophages of the supporting connective tissue. However, pigmentation of the vascular smooth muscle, as described in a later section, was extensive in blood

Fig. 1.—Small portion of skeletal muscle (gluteus maximus) showing necrosis of several muscle fibers, accompanied by considerable nuclear proliferation and nuclear pyknosis. Small leukocytes and macrophages are present in the vicinity of the necrotic fibers. Hematoxylin-eosin stain; × 430.

vessels throughout the skeletal muscles. In comparison with the rat, the monkey showed more widespread atrophy of skeletal muscle fibers but proportionately less pigment in these fibers and in adjacent macrophages.

Cardiac Muscle.—Only small and inconstant amounts of pigment were observed in the heart. In 2 monkeys small numbers of pigment granules were observed in the rather clear cytoplasm about the nuclei of the cardiac fibers. Occasional macrophages with pigment accumulations were found along the adventitia of the blood vessels and beneath the

endocardium. Except for some small areas of slight fibrosis, and an occasional necrotic fiber, the cardiac musculature was normal.

Smooth Muscle.—The most striking feature of the various organs and tissues examined was the pigment which had accumulated extensively within the smooth muscle cells forming the media of arteries and veins of all calibers (fig. 2), including arterioles; usually the aorta, the pulmonary vessels and the coronary vessels showed less pigment than other vessels. The granular pigment was sometimes limited to the paranuclear zone but was usually disseminated throughout the cytoplasm of the smooth muscle cells, the latter appearing somewhat swollen

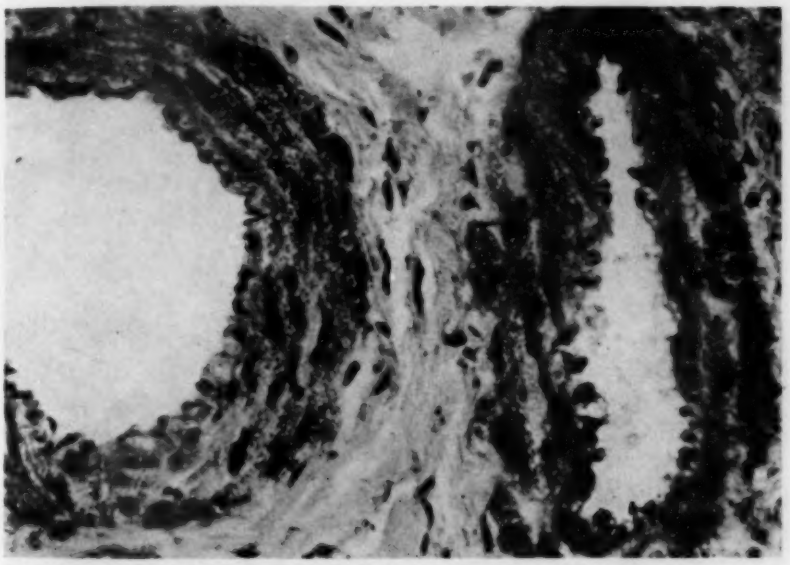

Fig. 2.—Small artery (left) and vein (right) showing abundance of pigment (appearing as black granules) within smooth muscle cells of the media. Acid-fast staining; × 430.

and edematous. As far as could be determined, the vascular endothelium was devoid of pigment.

There was considerable pigment within smooth muscle cells of the muscularis and the muscularis mucosae of the stomach, small intestine (fig. 3) and colon. These changes were more marked in the proximal than in the more distal portions of the digestive tract. The smooth musculature of the gallbladder, bronchi, bronchioles, urinary bladder and ducts of the epididymis was likewise involved to a variable degree; that of the splenic capsule and trabeculae was devoid of pigment.

Pigment was present in moderate amounts in many smooth muscle cells of the muscularis of the fallopian tube but was never identified

within those of the uterine myometrium. In both organs, pigment was abundant in the walls of blood vessels and in macrophages distributed throughout the muscularis and the mucosa. It is of interest in this connection that the uterine smooth muscle and the splenic trabeculae and capsule of vitamin E–deficient rats show rather pronounced pigmentation.[1b] Small amounts of pigment were observed in the epithelial lining of the uterus and tubes; on the basis of similar findings in other laboratory animals, this material is considered to be of normal occurrence and unrelated to the deficiency state.

Reticuloendothelial System.—The inguinal, internal iliac, mesenteric and tracheobronchial nodes were studied. All showed marked accumu-

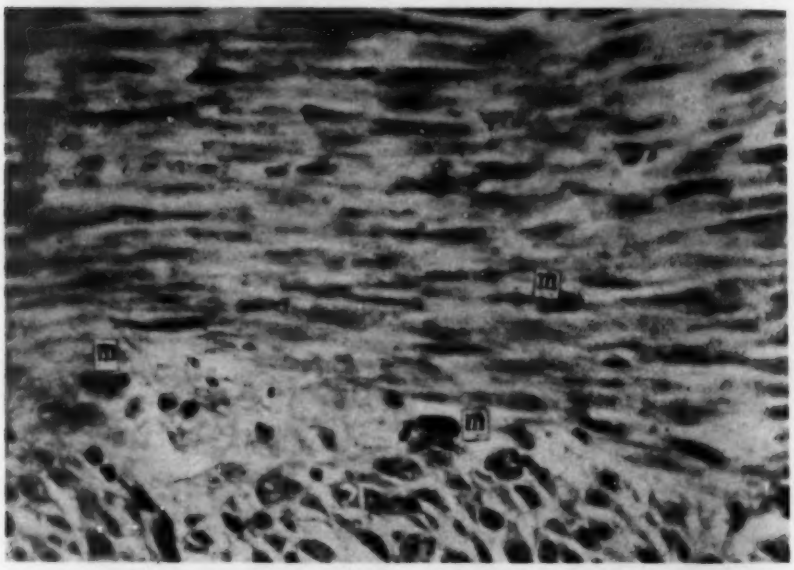

Fig. 3.—Small portion of the circular (above) and longitudinal (below) muscle coats of the duodenum, showing many fine pigment particles within smooth muscle cells and in occasional macrophages (*m*). Acid-fast staining; × 430.

lations of pigment granules and globules in the free macrophages and lining cells of the cortical and medullary sinuses (fig. 4). Sometimes the sinuses were completely filled by these cells. Pigment was also encountered in macrophages scattered throughout the lymph follicles and medullary cords. In some nodes the phagocytic cells contained considerable hemosiderin as well as pigment. Otherwise, the histologic picture was much the same in the various nodes examined. In general, the walls of blood vessels within the nodes and of those in the adjacent connective tissue (fig. 4) contained unusually large amounts of pigment.

In the spleen the accumulation of pigment was less extensive and somewhat more variable than in the lymph nodes. It was localized

principally in the lining cells and macrophages of the venous sinuses but was also abundant in macrophages of the red pulp (fig. 5). Here, too, hemosiderin and pigment occurred sometimes in the same cells and at other times in separate cells. No pigment could be identified in the smooth muscle cells of the capsule or trabeculae, or in the nonmuscular walls of the pulpal and trabecular veins.

In the liver the pigment was present in many Kupffer cells but rarely in hepatic cells. In the lung it occurred in a few alveolar phagocytes as well as in occasional connective tissue macrophages adjacent to the smooth musculature of the bronchi or in localized areas of inflammatory change.

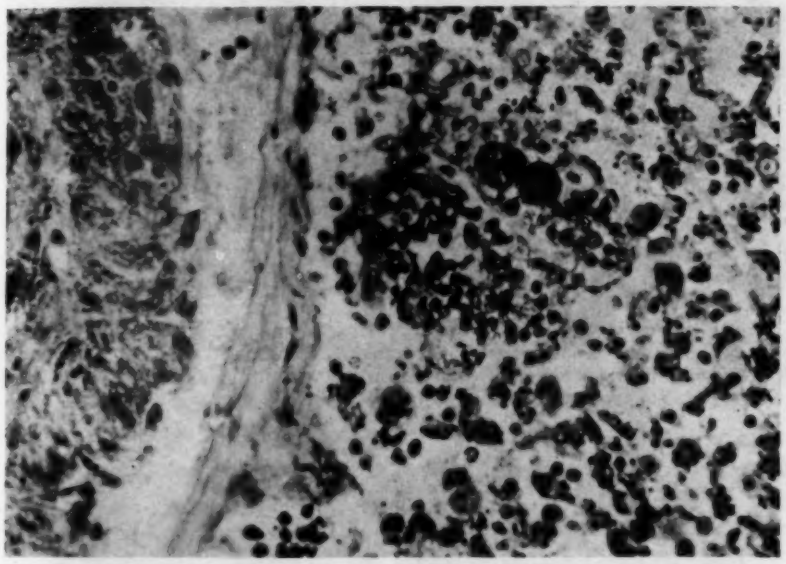

Fig. 4.—Cortex of a lymph node showing much pigment in several large fixed macrophages, in lining cells and free macrophages of the sinuses, and in the wall of a small artery just external to the capsule. Acid-fast staining; × 430.

The adrenal gland showed fine granules of pigment in some cells of the zona reticularis, in macrophages bordering the sinusoids of the cortex and in a few connective tissue macrophages of the medulla. Much of this pigment, like that of the ovary, considered in the following section, may occur normally and may not be specifically related to vitamin E deficiency. Small amounts occurred in the adrenal glands of 2 control monkeys.

Sex Glands.—The testes of 1 male were quite infantile; those of the other showed only a few seminiferous tubules in which secondary spermatocytes or spermatids were differentiated. No pigment was

observed in the seminiferous tubules or in the interstitial tissue. The ducts of the epididymides were small and empty. The general picture was one of immaturity rather than one of degenerative change.

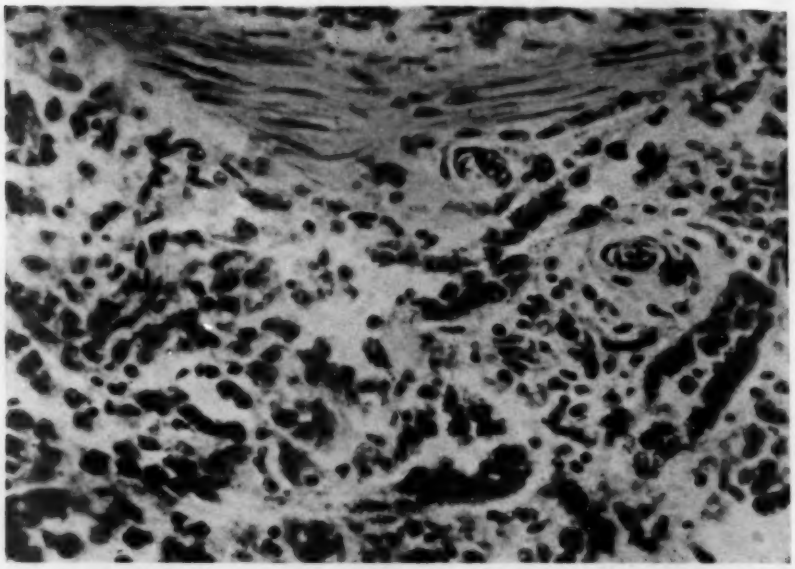

Fig. 5.—Portion of spleen showing absence of pigment in the smooth muscle cells of the trabecula but extensive accumulations of this material in fixed macrophages lining the venous sinusoids and distributed throughout the splenic cords. Acid-fast staining; × 430.

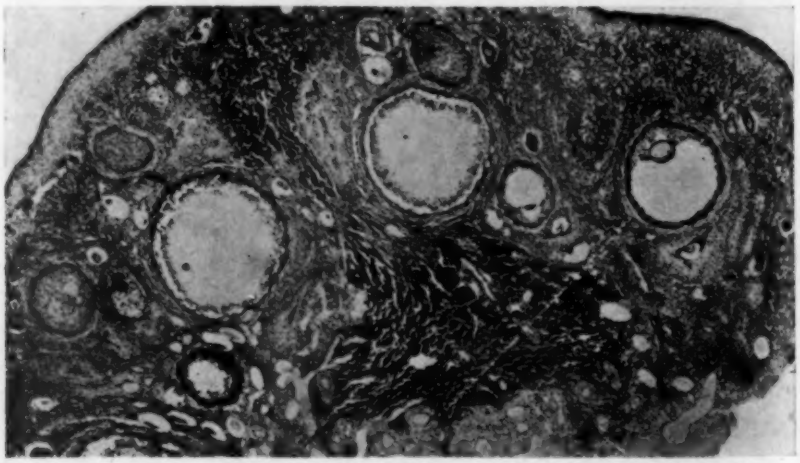

Fig. 6.—Part of ovary showing two regressing corpora lutea, composed of compact masses of lutein cells and macrophages, both containing large amounts of pigment. Acid-fast staining; × 30.

The ovaries of both females contained several large corpora lutea in process of regression. These stained brilliantly with carbolfuchsin (fig. 6). The large and rather vacuolated lutein cells were uniformly filled with granules and globules of acid-fast pigment. Pigment-laden macrophages, somewhat smaller in size and less vacuolated, were present between the lutein cells and were abundant throughout the stroma of the ovary, especially in the vicinity of follicles that were in advanced stages of atresia. Only a relatively small proportion of the acid-fast material in lutein cells and macrophages showed the definite affinity for iron-hematoxylin which characterized that in smooth muscle cells. Further observations are necessary to determine how much of this ovarian pigment was due to vitamin E deficiency and how much can be considered normal in occurrence.

The ovaries of our control monkeys, because of sexual immaturity, contained no corpora lutea; moreover, they contained no cells with acid-fast pigment. On the other hand, Rossman [5] has observed in regressing corpora lutea and macrophages in the ovaries of normal monkeys a pigment giving a positive Feulgen reaction and staining with sudan III in paraffin sections; he has given the designation "lipolutein" to this material. Through the courtesy of Dr. George Corner, director of the department of embryology of Carnegie Institution of Washington, Baltimore, we have had the privilege of examining some of Rossman's histologic preparations. The ovarian picture closely resembles that seen in our material stained according to the methods used by Rossman. In the ovaries of normal rats a similar but more limited pattern of pigment distribution occurs; with vitamin E deficiency the amount of pigment deposited in the ovary increases markedly.[6] Other observations [2] indicate the same to be true of other rodents. Because of the limited histologic material available, we are unable to determine with certainty whether the ovary of the vitamin E–deficient monkey responds in a similar manner. Little is known concerning the chemical nature of the acid-fast pigment arising as a result of vitamin E deficiency and that occurring in limited amounts normally in the ovary, the adrenal gland and certain epitheliums of the male and female reproductive tracts. The latter seems related in some unknown manner to lipids arising in cells of these organs during or subsequent to active production of steroid hormones. The former may represent unsaturated fatty acids that have undergone peroxidation and polymerization because of inadequacy of an important antioxidant, vitamin E, in the cytoplasm of the cells involved.[7]

5. Rossman, I.: Contrib. Embryol. **30**:99, 1942.

6. Mason, K. E., and Emmel, A. F.: Yale J. Biol. & Med. **17**:189, 1944.

7. Mason, K. E.; Dam, H., and Granados, H.: Anat. Rec. **94**:265, 1945.

Kidney.—Pigment was seen in a few macrophages between the renal tubules and, in 1 animal, as intracellular granules within cells of the proximal convoluted tubules. Fuchsinophil granular deposits occurred in the lumens of some secretory and collecting tubules, suggesting excretion of pigment by the kidney.

COMMENT

The present study provides evidence that at least one of the primates, the Macaca rhesus monkey, responds to vitamin E deprivation in much the same manner as do other mammalian species. It also emphasizes again the dysfunctions occurring in both striated and smooth muscle cells when these are deprived of vitamin E, as reflected in the intracellular accumulations of a yellowish brown fluorescent inert acid-fast pigment. That this pigmentation of tissue would not have occurred in monkeys fed the same deficient diet supplemented with vitamin E remains to be demonstrated but may be inferred from comparable observations on other laboratory animals; for a similar pattern of pigment accumulation noted in the rat [1b] and in the hamster, the cotton rat and the mouse [2] is readily prevented by feeding mixed natural tocopherols. In view of the evidence that its formation is dependent on the presence of unsaturated fatty acids as well as on a deficiency of vitamin E in the diet, it is rather surprising that the diet used in the present study, containing only 4.2 per cent lard and 0.57 per cent cod liver oil as added fat, produced such extensive formation of pigment. This may be due, in part, to the much longer feeding period employed in the studies with monkeys. The observation that considerable acid-fast pigment occurs in human tissues, reported by Pappenheimer and Victor,[8] is of particular interest in connection with the observations presented here.

The acid-fast pigment in the vitamin E–deficient rat seems to be released to macrophages from smooth muscle cells without appreciable loss of their structural integrity but from skeletal and cardiac muscle cells in the course of their disintegration.[1b] Our findings in the monkey are in reasonable accord with these interpretations. While the skeletal muscles of the deficient monkeys showed relatively little pigment in proportion to the dystrophic changes observed, this may be related to the low content of unsaturated fatty acids in the diet or to species differences.

Brief reference should be made to the striking and unexplained differences in the pattern of distribution of this pigment, especially in the extent to which the smooth musculature of different organs is involved, in the monkey and in other species studied. For instance, pigmentation of the smooth muscle of blood vessels constitutes a striking

8. Pappenheimer, A. M., and Victor, J.: Am. J. Path. **22**:395, 1946.

feature in the monkey and is widespread in the hamster but has been observed in only a few vessels of the rat and then only after prolonged deficiency. Similar changes of intestinal muscle are easily induced in the monkey, the hamster and the dog but are difficult to produce in the rat. On the other hand, changes of uterine smooth muscle are rather characteristic of the rat and have not been observed in other species. Accumulation of pigment in reticuloendothelial cells of the lymph nodes and spleen is common to all animal types studied but is especially marked in the monkey. It has been impossible to determine whether all of this material is carried and deposited there by macrophages of the connective tissues, or whether some of it may be absorbed directly from the lymph and blood streams or may arise through abnormal autoxidation of lipids within these cells. The possibility that the pigment of vascular smooth muscle represents material absorbed as such from the blood stream seems unlikely unless the mechanisms involved here are quite different from those prevailing in smooth muscle elsewhere. Whether these vascular changes were associated with circulatory dysfunctions sufficient in magnitude to account for the unexplained decline and death of the monkeys and whether the response of man to vitamin E depletion resembles in any way that shown by the monkey remain to be determined by further investigation.

SUMMARY

Four young monkeys that had been reared for two to two and one-half years on a vitamin E–deficient diet showed extensive accumulations of an acid-fast pigment in smooth muscle cells of the blood vessels, stomach, intestines, gallbladder, bronchi, urinary bladder and fallopian tube, in the reticuloendothelial cells of lymph nodes and spleen and in many connective tissue macrophages. There was gross and histologic evidence of dystrophic changes in skeletal muscles, with deposition of small amounts of pigment in the fibers. Cardiac muscle fibers contained some pigment but showed little or no evidence of damage. On the basis of similar findings in other laboratory animals, these observations are presented as evidence that a state of vitamin E deficiency can be induced in the monkey.

EFFECTS OF PODOPHYLLIN AND OF COLCHICINE ON NORMAL SKIN, ON CONDYLOMA ACUMINATUM AND ON VERRUCA VULGARIS

Pathologic Observations

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IN 1942 Kaplan [1] described the therapeutic effects of resin of Podophyllum N. F. (podophyllin) as applied topically to condyloma acuminatum. Subsequent reports fully confirmed his claim concerning the efficacy of this drug. That small epithelial tumors disappear temporarily or permanently under the action of caustics is an old and familiar observation, but the phenomenon of certain neoplasms responding to a resinous substance whose original use was that of a cathartic raises many intriguing problems. The mode of action of podophyllin is not known. Culp and Kaplan [2] suggested that the irritative action of the drug causes spasm of small vessels, resulting in ischemic necrosis and sloughing of the tumor. No evidence was offered in support of this hypothesis.

In the course of studies on the curative action of podophyllin as applied to condyloma acuminatum we have elsewhere [3] presented clinical and experimental data and a brief summary of the histologic observations. It was observed that this drug produced certain cellular changes similar to those seen after the administration of colchicine.[4] Colchicine, as well as podophyllin, was therefore used in the treatment of condyloma acuminatum. The purpose of the present communication is to present the histologic changes following the use of these drugs in greater detail than was possible in the earlier paper.

A portion of this work was done at the William Beaumont General Hospital, El Paso, Texas, while both authors were in the Army of the United States.

From the laboratory of the Illinois Masonic Hospital and the department of pathology of the University of Illinois College of Medicine, Chicago (Dr. King), and the department of dermatology of the Johns Hopkins University School of Medicine, Baltimore (Dr. Sullivan).

1. Kaplan, I. W.: New Orleans M. & S. J. **94**:388, 1942.
2. Culp, O. S., and Kaplan, I. W.: Ann. Surg. **120**:251, 1944.
3. Sullivan, M., and King, L. S.: Arch. Dermat. & Syph., to be published.
4. King, L. S., and Sullivan, M.: Science **104**:244, 1946.

REACTION OF NORMAL SKIN TO PODOPHYLLIN

As described in the previous communication, podophyllin made up in liquid petrolatum, was applied to normal skin and mucous membranes. Patch tests were applied to the skin of the forearm. In one group of 100 patients 30 per cent showed a positive reaction of the skin at the end of twenty-four hours. In another group of 100 patients 69 per cent had a positive reaction after forty-eight hours. The reactions subsided in four to seven days. In 9 cases specimens of skin were taken for biopsy, through the affected portion of the skin, at one, two, and seven days after the application of the drug.

To study the effect of podophyllin on normal mucous membrane, 6 patients scheduled for circumcision received preliminary applications of the drug twenty-four or forty-eight hours before operation. The excised foreskins were examined histologically.

Our descriptions of the reactions of normal skin and mucosa are based on these 15 cases. All stages obviously are not represented, since carefully timed intervals are feasible only when experimental animals are used. Although abundant experimental material is available to us at present, the results observed in animals reveal certain differences. Since experiments are still in progress, the results will not be drawn on in this communication but will be reported separately.

A well developed histologic reaction, appearing twenty-four hours after application of the drug and lasting about three days, reveals the following features: In many cases the surface is covered by a narrow layer of loosely woven hyperkeratotic material, not significantly increased in amount. The normal granular layer, with its flattened cells, is also narrow and is well defined. The upper prickle layer, however, may show definite changes. The cells are large and plump; intercellular bridges frequently are absent, while cell membranes are accentuated and heavily stained (fig. 1*A*). Numerous fine keratohyaline granules may be visible within these large, rounded cells. The cytoplasm stains rather palely, and a delicate linear reticulation is seen. Faint dark pink lines, suggestive of tonofibrils, may irregularly permeate the cells and are sometimes in a concentric circular arrangement. The intervening cytoplasm exhibits a pale color, resembling a bubbly vacuolation within a reticulum. This is probably not a true vacuolation but rather a rarefaction of cytoplasm. The delicate fibrils frequently extend to the thickened cell membrane but do not cross from cell to cell. The fine keratohyaline granules appear situated in the interstices between fibrils.

Many cells in the upper prickle layer reveal genuine vacuolation and have a large clear perinuclear halo. In such cells the nucleus is slightly shrunken and darkly stained, with chromatin compact and the nuclear pattern obscured.

In the deeper prickle cell layer there is a great variety of cell change. A characteristic cell, illustrated in figure 1 *A*, is large and pale, and definitely but faintly basophilic. The cytoplasm is composed of a promi-

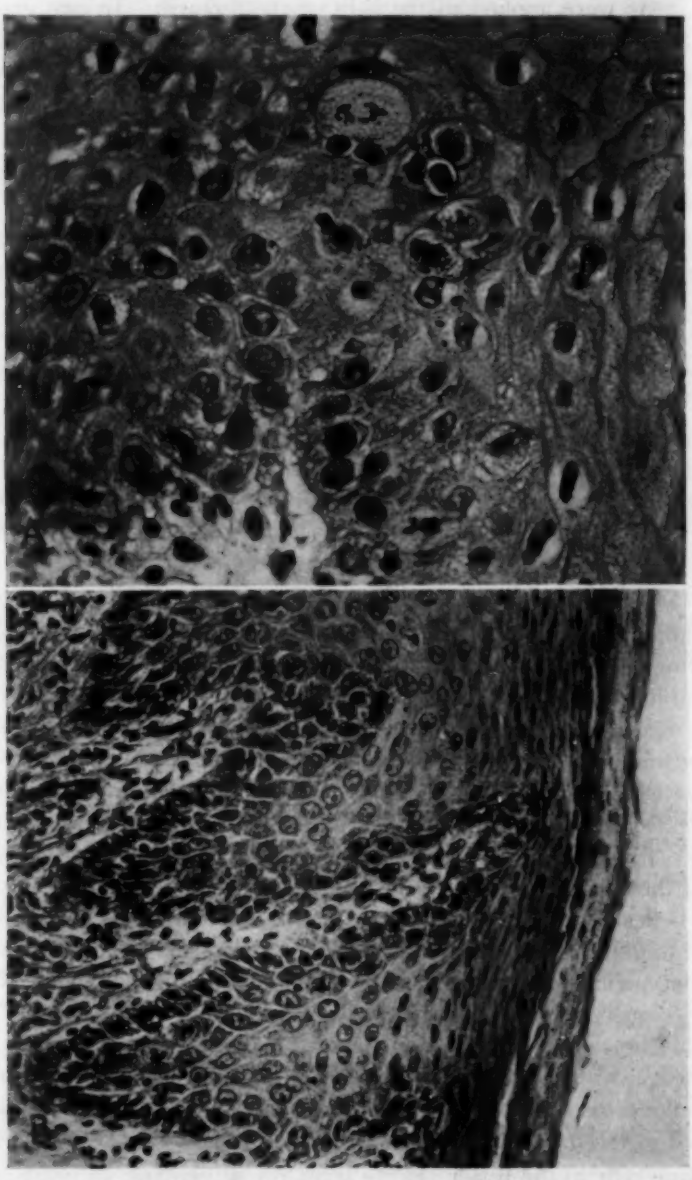

Fig. 1—*A*, effect of podophyllin applied to the skin of the forearm. Note a characteristic "podophyllin cell," surrounded by pyknotic cells. The accentuation of cytoplasmic membranes is also noteworthy.

B, prepuce twenty-four hours after application of podophyllin. Numerous distorted mitotic figures are visible near the basal layer.

nent, though faintly staining, reticulum. No nucleus is present, but nuclear material is seen as dispersed blue-staining dots or rods, which are usually symmetrically disposed within the cell, suggesting distorted mitotic figures. In some cells the entire confines are filled with reticulated cytoplasm; in others there is a variable degree of peripheral vacuolation, with central condensation of cytoplasm. The nuclear material, in the form of fine threads or granules, may be concentrated in the center or may exhibit symmetric distribution in the poles of the cells. The arrangement and the structure of the chromatin do not simulate normal mitotic phases but appear as parodies of mitosis (fig. 1 *B*).

The opposite extreme of distortion is represented by cells with bright eosinophilic cytoplasm and pyknotic or karyorrhectic nuclei. Several are seen surrounding the large pale cell in figure 1 *A*. These cells with the pyknotic nuclei show a considerable range of morphologic variation. Cytoplasm of solid texture may fill the cell confines; or peripheral vacuolation may be prominent, leaving a clear space between the cell membrane and the centrally aggregated eosinophilic cytoplasm; or the vacuolation may be irregular, with lacunas alternating with wisps of cytoplasm. The nucleus may be represented by a single solid basophilic structure, or it may take the form of several irregular karyorrhectic fragments.

Between these two extremes of cellular appearance there are many forms which can be interpreted as intermediate gradations. Thus, the nuclear material may be broken up into so many and variously disposed fragments that it is not possible to distinguish distorted mitosis from bizarre karyorrhexis. The cytoplasm may exhibit all shades of staining reaction from frank basophilia, through subtle degrees of purple, to outspoken eosinophilia. In still other variations the cytoplasm is concentrated in the center of the cell, with vacuolar spaces intervening next to the cell membrane, but with delicate strands of cytoplasm traversing the clear spaces. Nuclei preserve their general form but may be moderately shrunken, with intensification of staining and loss of clarity of nuclear detail, yet definitely not pyknotic. Cell membranes may be accentuated and thickened. The intercellular spaces surrounding such altered cells may or may not be preserved. In some instances they are exaggerated. These changes (fig. 2 *A*), most prominent in the lower prickle layer, may occasionally be found in the basal layer, while in other instances the basal layer is preserved intact. There are numerous variable alterations, consisting of changes of cell size and shape, variations of nuclear size, multiplication of nucleoli, vacuolation of cytoplasm, widening of intercellular spaces and occasional normal mitotic figures. There is no constancy in alterations of the basal layer.

In the corium there are slight edema and scanty round cell infiltration, principally perivascular. Inflammatory changes are more prominent in

sections of foreskin than in sections taken from the sites of patch tests. No vascular thrombi have been noted.

In the later stages, seven days after the initial application of podophyllin, when clinical signs of reaction have subsided, changes are relatively few. Three specimens are available for study. On the surface there is an increased amount of keratinized material, frequently of dense character, together with inconstant patches of parakeratosis. The keratohyaline granular layer is accentuated and more prominent than normal. Mild acanthosis is observed. Occasional pyknotic eosinophilic cells may be seen, of the type described in a foregoing paragraph, sometimes surrounded by whorls of well preserved cells. Some perinuclear vacuolation can be seen. Some nuclei of the basal cells may be enlarged and elongated, with a heavy chromatin content, while others are shrunken and darkly stained. Vacuolation of the basal layer is widespread. Persisting mild edema and perivascular round cell infiltration are observable in the upper part of the corium. Our series of human specimens is not sufficiently closely graded to permit following in detail the fate of the altered cells so prominent at twenty-four and forty-eight hours. It appears, however, that an essentially normal skin is reconstituted, even though at seven days faint traces of dyskeratosis and irritation can be observed.

CONDYLOMA ACUMINATUM TREATED WITH PODOPHYLLIN

Eighty patients with condyloma acuminatum were treated with podophyllin suspended in liquid petrolatum or dissolved in alcohol. Excellent results were obtained except in 3 patients with chronic, partially cornified tumors. Where clinical success was attained, involution progressed rapidly, and tumors in different stages of involution were excised. Altogether, 29 separate condylomas from 13 patients were studied, representing various phases of successful involution, and some examples of resistant nonresponsive lesions. In addition, there were 13 condylomas from 5 patients who had been treated with colchicine.

In the podophyllin-treated tumors the biopsies disclosed cytologic changes comparable to those seen in similarly treated normal skin. Figure *2 B* illustrates the microscopic appearances present twenty-four hours after application of the drug. In the lower portion of the prickle layer are several distorted cells, whose chromatin material is broken up or clumped. The cells are sharply ballooned and swollen, with massive peripheral vacuolation and central irregular condensation of cytoplasm. A few pyknotic eosinophilic cells are present. One cell shows chromosome-like dispersion of the nuclear material. Most of the cells in the field show enlarged nuclei, with enlargement or multiplication of nucleoli and distortion of nuclear chromatin pattern. Reticulation and minor degrees of cytoplasmic vacuolation are apparent in most cells. Edema and slight leukocytic infiltration are visible in the underlying connective tissue.

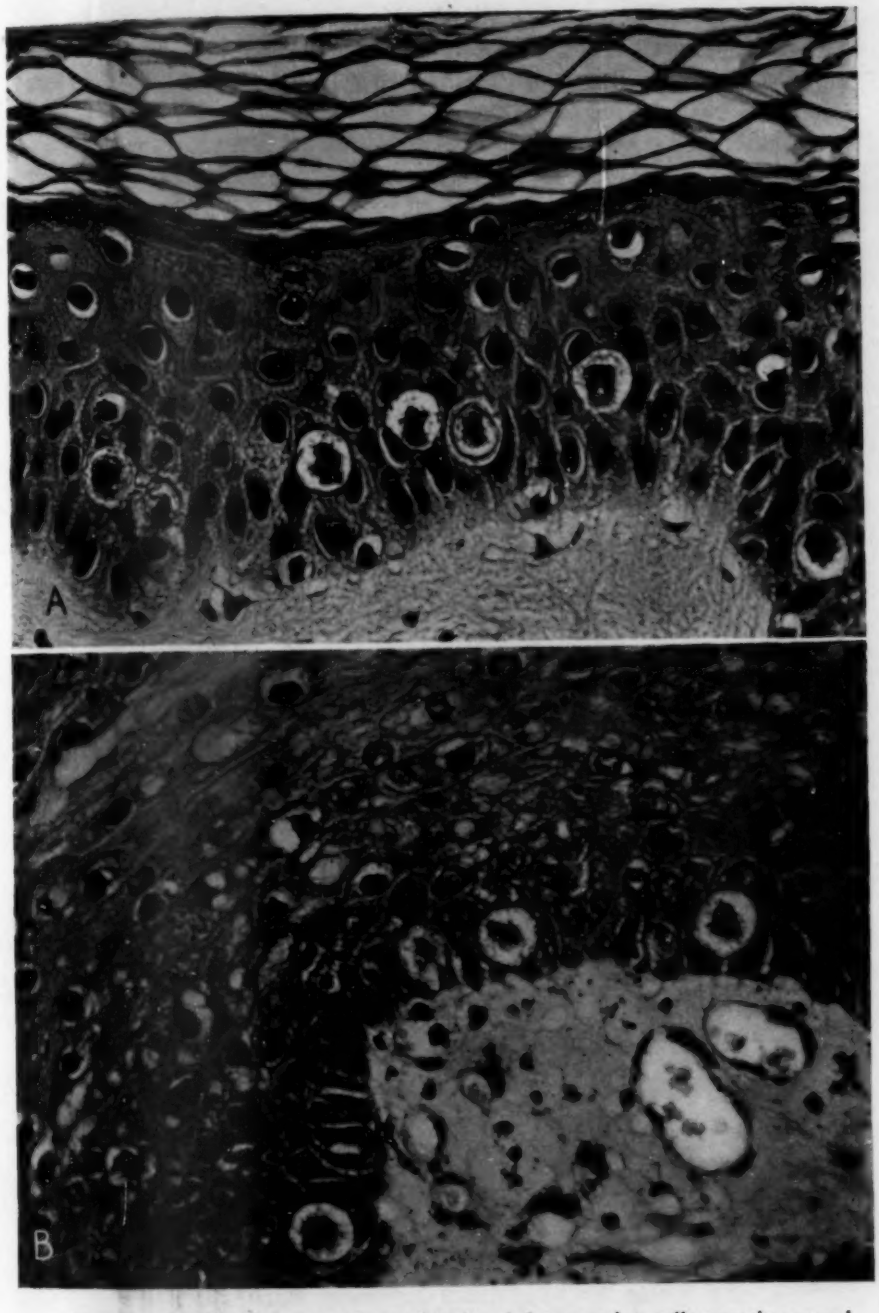

Fig. 2.—*A*, different types of vacuolated and degenerating cells seen in normal skin to which podophyllin has been applied.

B, condyloma acuminatum twenty-four hours after application of podophyllin. Note the similarity to the deeper-lying vacuolated cells of *A*.

The accentuation of the cytoplasmic membranes of the more superficially lying cells is seen in figure 3 *A*, together with the loss of intercellular bridges and cytologic changes of types already described. The

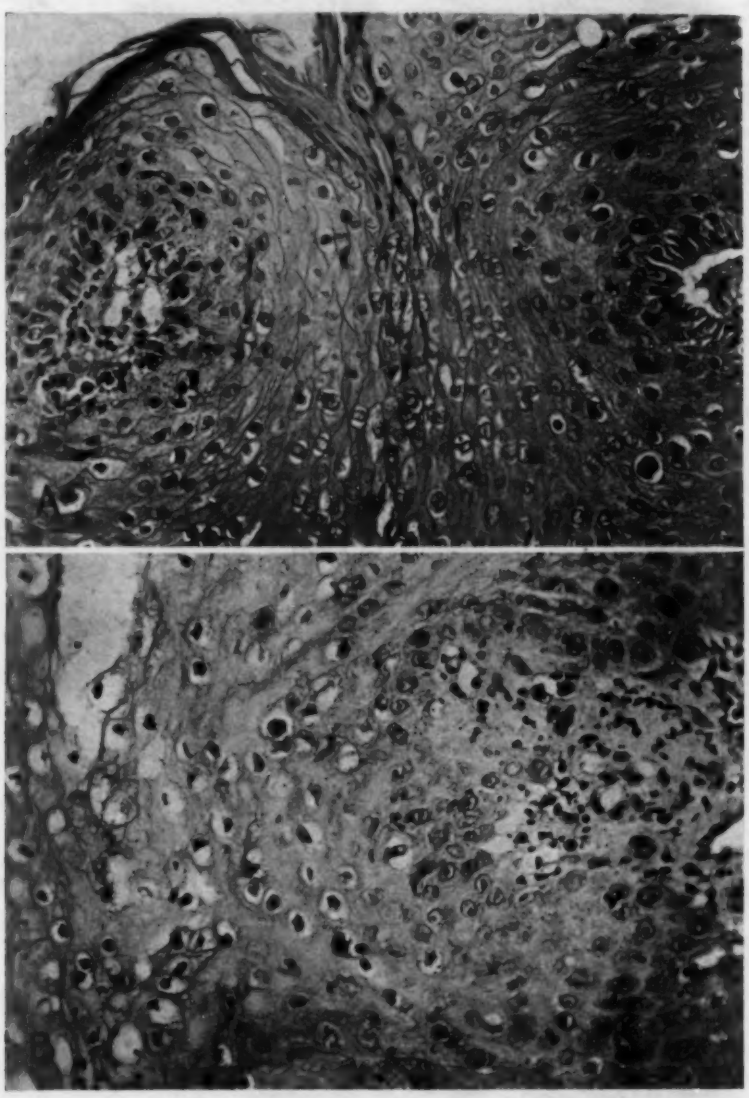

Fig. 3—*A* and *B*, condyloma twenty-four hours after a single application of podophyllin. Various forms of pyknosis, vacuolation and degeneration are prominent, as described in the text.

distortion of cell structure and the variable types of cytoplasmic vacuolation are apparent in figures 3 *A* and *B*, both of which are from twenty-four hour specimens.

Figure 4 *A* shows the residual epithelium of a condyloma which had received two applications of the resin seventy-two and forty-eight hours before biopsy. Clinically the lesion was represented only by a flat whitened patch. Histologically, virtually every cell shows severe degenerative phenomena, with shrinkage of nuclei or pyknosis and karyorrhexis, severe cytoplasmic vacuolations and marked accentuation of cell mem-

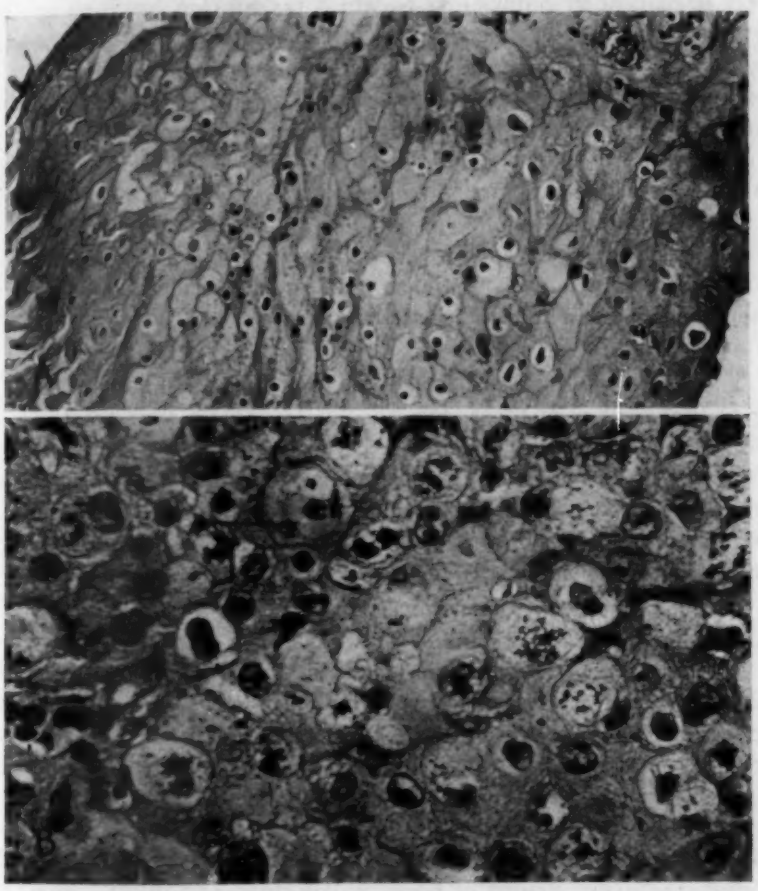

Fig. 4—*A*, condyloma showing complete involution after two applications of podophyllin. The drug had been applied seventy-two and forty-eight hours before excision. Virtually every cell reveals the degenerative changes described in the text. B, condyloma after three daily applications of colchicine. "Colchicine cells" are extremely numerous.

branes. Not visible in the photograph is the fine dusting with keratohyaline granules which occurs in the large pale plump cells of the midgranular layer. The so-called "podophyllin cells," illustrated in figure 1 *A*, are not in evidence. In other excised condylomas the cells in the basal and lower prickle layers are better preserved but exhibit exten-

sive nuclear swelling and distortion, enlargement of nucleoli, vacuolation of nuclei and varying degrees of hyperchromatism. A few "podophyllin cells" are occasionally present.

It should be pointed out that these curious large cells with changes resembling aborted or atypical mitoses, which we designate as "podophyllin cells" and which are illustrated in figure 1 *A*, are relatively infrequent in condylomas to which podophyllin has been applied. Cytologic changes of diverse types are widespread, but the peculiar break-up of nuclear material, so different from simple karyorrhexis in eosinophilic cells, is seen only occasionally. On the other hand, when condylomas are treated with colchicine instead of podophyllin, this type of change may be extensive. In figure 4 *B* is seen a section of a condyloma which regressed after three daily applications of colchicine and which was excised on the fourth day. Fully half of the cells of this field reveal dispersion of chromatin threads within swollen, reticulated cytoplasm. The dispersion is irregular, and under the microscope one can observe some basophilic material that has been extruded through the cytoplasmic wall.

These cells we designate "colchicine" or "podophyllin" cells, according to the agent used to produce them. In essence they are identical. The principal histologic difference between the two drugs is quantitative only. With colchicine these peculiar cells are far more numerous than they are with podophyllin. But both drugs produce abundant eosinophilic pyknotic cells, as well as others with varying degenerative nuclear and cytoplasmic changes.

Histologic study of condylomas that failed to respond clinically to applications of the drug reveals certain facts of considerable interest. In 1 patient with perianal condylomas the lesions were initially moist and pink. After applications of podophyllin they became dry and white, but they decreased only slightly in size. Representative tumors, excised three days and six days after a single application, show morphologic features approximating verruca vulgaris rather than condyloma acuminatum. There is a heavy layer of keratin, with patches of parakeratosis contained therein. The granular layer is broad and prominent, but the cells of this layer, instead of being well formed and intact, are highly vacuolated and frequently show pyknotic nuclei. The keratohyaline granules are massive and are occasionally situated within the cytoplasmic vacuoles. The prickle and basal layers exhibit no significant changes. The sections suggest that the action of podophyllin increased the cornification, instead of causing degeneration of the cells.

Two other treated tumors are in a different category. The clinical response was much slighter than was expected. One tumor received a single application of podophyllin and was excised twenty-four hours later. The second was treated with colchicine on two successive days

and was removed forty-eight hours after the second application. In both of these, although involution was relatively slight, histologic examination revealed abundant change indicative of drug activity. Whether, if not excised, these lesions would have undergone complete involution in time is of course problematic. But that such would be the case seems entirely plausible. These two results should probably be called delayed reactions and not failures. The feature of interest is the presence of abundant cytologic change before a significant clinical effect is manifested.

VERRUCA VULGARIS TREATED WITH PODOPHYLLIN

Podophyllin and colchicine when used in the treatment of verruca vulgaris were clinically disappointing. Verrucae which had been treated with these drugs were taken for biopsy from 19 patients. The number of separate verrucae totaled 30. Specimens were excised after both single and multiple applications. For the most part, no clinical improvement whatever could be noted. In some cases the margin between skin and verruca showed some reddening, and in 1 instance there was apparent early ulceration at the margin of the verruca. Microscopic examination proves equally disappointing. The prominent hyperkeratosis and parakeratosis are completely unaffected by the drug. The broad keratohyaline layers may show cytoplasmic vacuolation but not to a greater degree than is seen in many untreated control verrucae. The prickle layer, characteristically wide, cannot be distinguished from control material, while the basal layer shows no significant alterations. Occasionally, however, the lateral edge of the verruca, where the keratin layer is thinnest, or the normal skin immediately adjacent to the lesion shows cytologic changes. "Podophyllin cells" in small numbers, together with scattered pyknotic elements, and varying types of severely vacuolated cells can be observed. The histologic changes are not qualitatively different from those already described.

The occasional reaction visible at the margin of a specimen is in consonance with the clinical observation that a few treated warts, without any shrinkage in size, became detached at their bases.

COMMENT

The cytologic effects of podophyllin are similar to those of colchicine, as has already been reported.[4] There is an extensive literature on colchicine and related drugs, the review of which is not within the scope of this paper. Certain key contributions, however, may be cited.[5]

5 Ludford, R. J.: Arch. f. exper. Zellforsch. **18**:411, 1936. Lits, F. J.: Arch. internat. de méd. expér. **11**:811, 1936. Dustin, A. P.: Arch. f. exper. Zellforsch. **22**:395, 1938. Brues, A. M., and Jackson, E. B.: Am. J. Cancer **30**:504, 1937. Chodkowski, K.: Protoplasma **28**:597, 1937.

Colchicine is merely one of a small group of substances which exert profound effects on cell division. In the literature these drugs have been administered by injection, with effects manifested over the entire body. Studies with tissue culture have also been made. But the present paper is concerned only with topical application of podophyllin and of colchicine to normal skin, condylomas and verrucae. Consequently, the results described in the literature cannot be uncritically adopted in the present studies, because of the difference in mode of administration. It is apparent from our studies that podophyllin can penetrate the normal skin and moist condylomas but that massive amounts of keratin such as are found in the common warts of the skin (verruca vulgaris) offer a barrier to its penetration and action.

The changes produced by podophyllin are of diverse types. Some cells are killed outright, as evidenced by eosinophilic shrunken cytoplasm and pyknotic or karyorrhectic nuclei. Other cells undergo morphologic disturbance which we interpret as abortive mitosis of irregular type. They are seen in relatively small numbers. Still other cells reveal a wide variety of changes which can best be interpreted as of degenerative character. In the beginning of these studies it was thought that several varieties of altered cells could be clearly isolated and carefully distinguished. Some sorts of altered cells, described in the text, occur with frequency and regularity. But so many intermediate and transitional forms were observed that we adopted the concept of a continuum of change in which the extremes are pyknosis and abortive mitosis.

A problem arises concerning the specificity of these various changes. The peculiar mitotic figures which we designate as "abortive" (produced in small numbers with podophyllin, in larger numbers with colchicine) may be considered as reasonably specific for a small group of drugs, among which colchicine has been studied most extensively. But at this point all claim for specificity must cease. Pyknosis is obviously nonspecific. The varying types of cytoplasmic vacuolation that we have described cannot be accurately classified. Two main types, perinuclear and peripheral vacuolation, occur, with gradations in between. The amount, the disposition and the tinctorial reaction of the preserved cytoplasm also vary. Along with the cytoplasmic changes, the nuclei present alterations in size and shape and in disposition and amount of chromatin, as well as nucleolar variations.

Under low power of the microscope a general pattern may be recognized, which we are accustomed to designate as "podophyllin effect." But cells of similar type can also be found, on careful examination, in occasional untreated condylomas or in tumors treated with salicylic or with trichloroacetic acid. The changes in the latter cells are not necessarily identical with the changes which we have described and illus-

trated, but a fundamental kinship is suggested. To be sure, only in the drug-treated lesions have we found such cells in considerable and significant numbers, but careful search will show rare similar cells in untreated lesions.

In the classic descriptions of verruca vulgaris [6] peculiarly vacuolated cells receive mention. Waisman and Montgomery,[7] in their study of verruca plana, epithelial nevus and epidermodysplasia verruciformis, described and illustrated various degenerative cell forms not dissimilar to many of the changed cells which we have observed. Sullivan and Ellis,[8] as well as Wise and Satenstein,[9] describing epidermodysplasia verruciformis, also comment on vacuolated forms. These alterations are by no means duplicates of what we have observed, nor do they occur in the same layers of the epidermis, but they suggest a possible relationship.

The squamous epithelial cell as it evolves from the basal layer to its final keratinization may be subjected to innumerable influences reflected in morphologic alteration. From the altered appearance we can justifiably conclude that there has been an interruption of the normal metabolic processes, but we cannot necessarily infer what that interruption has been. In the present studies, the extensive changes in the deeper layers of the epidermis we consider to be of greater significance than vacuolar or pyknotic changes in the upper layers. We infer that pathologic changes in the lower layers, where growth energy is greatest, are indicative of far greater metabolic disturbance than similar and sparser changes in the upper layers.

From our studies to date we conclude that podophyllin, as well as colchicine, locally applied, exerts a profound effect on the function of the cell, leading to extensive degenerative change. In some cells there is a stimulation leading to disorderly and irregular mitosis. This is probably also a degenerative manifestation, merely a special instance of drug action, perhaps dependent on the physiologic state of the particular cell. In condylomas the cell degeneration leads to regression of the tumor. Inflammatory changes of the corium may occur but are not directly responsible for the melting away of the tumor, and the drug's action on the cells is not mediated by vascular alterations. In just what way these drugs affect cellular metabolism there is no evidence from the present study to show.

Detailed experimental investigation is in progress and will be reported at a later date.

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6. Lipschutz, B.: Arch. f. Dermat. u. Syph. **148**:200, 1922. Gans, O.: Histologie der Hautkrankheiten, Berlin, Julius Springer, 1928, vol. 2, pp. 112-121.
7. Waisman, M., and Montgomery, H.: Arch. Dermat. & Syph. **45**:259, 1942.
8. Sullivan, M., and Ellis, F. A.: Arch. Dermat. & Syph. **40**:422, 1939.
9. Wise, F., and Satenstein, D. L.: Arch. Dermat. & Syph. **40**:742, 1939.

SUMMARY

Podophyllin and colchicine when topically applied to squamous epithelium cause profound morphologic disturbances. The most characteristic change is the production of enlarged, swollen cells with finely reticulated, palely basophilic cytoplasm and dispersed chromatin material which shows some type of chromosomal arrangement. Other changes, more frequently seen, such as eosinophilic cells with pyknotic nuclei, various forms of cytoplasmic vacuolation and nuclear alterations, are described in detail but are not claimed to be specific. These are considered as primarily degenerative in character, reflections of the impairment of cellular metabolism produced by the immediate action of the drug. These pathologic conditions are seen in normal skin and in condyloma acuminatum when treated with podophyllin or with colchicine. The regression of the condyloma is in general correlated with the morphologic changes described. The drugs are inactive when applied to a highly keratinized structure such as verruca vulgaris.

AGE AND WEIGHT AS FACTORS IN THE DEVELOPMENT OF EXPERIMENTAL CHOLESTEROL ATHEROSCLEROSIS IN RABBITS

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VARIOUS investigators suggested that the spread and the degree of experimental cholesterol atherosclerosis of rabbits more or less parallel the degree of hypercholesteremia. The blood cholesterol level in turn depends largely on the length of time this substance had been fed to the animals. There is a limit to the quantity of pure cholesterol one can feed to a rabbit; the only restriction of the duration of the feeding experiment, however, is the life span of the rabbit, which usually is twenty-four to thirty months.

Protraction of the period of cholesterol feeding harbors fallacies one should be aware of. With advancing age, physiologic and sometimes pathologic changes develop in the rabbit which may influence the course of the experiment, its results and possibly its interpretation. Spontaneous alterations resembling atherosclerosis were observed in old rabbits on occasion.

In many a valuable report one misses information about the age and the weight of the experimental animals. These omissions render imitation of the experiments for verification or as a working basis for further research difficult if not impossible.

MATERIALS AND METHODS

In the study the weight of each rabbit was controlled daily and the dose of cholesterol fed adjusted so that 0.1 Gm. was given per 600 Gm. of body weight. Chemically pure powdered cholesterol (Merck) was weighed out on an analytic balance and filled into gelatin capsules. Size 5 capsules were used for quantities below 0.1 Gm., size 2 for amounts from 0.1 to 0.5 Gm. and size 00 for 0.5 Gm. Some rabbits had to be given two or three capsules at a time. All animals took the feeding well, none developed diarrhea, and all survived. The rabbits were fed Purina rabbit chow, and fresh vegetables were added (lettuce, turnips, spinach, carrots). The experiment was conducted from May to July. Blood cholesterol levels of all rabbits were checked by a colorimetric modification of Bloor's method at the onset of the experiment and weekly during the period of observation.

Thirty-two rabbits (1 through 32) were used in the study: One half were males (1, 3, 5, etc.) and one half were females (2, 4, 6, etc.); one half were gray and one

From the Wilmington General Hospital.
This article is the third of a series (Arch. Path. **39**:11 and 16, 1945).

half were albinos. Twenty-four animals were killed at the end of their feeding periods; the 8 control animals were killed at the end of the experiment. According to their age and weight, the rabbits were divided into four groups A, B, C and D. The animals in each group were comparable, being of about the same

TABLE 1.—*Outline of Experiment*

Group of Rabbits *	Age, Weeks	Weight, Gm.	Blood Cholesterol, Mg. per 100 Cc.	Dose of Cholesterol, Gm.	Rabbits † Fed Cholesterol the Given Number of Days						Controls After 60 Days	
					30 Days		45 Days		60 Days			
A	5	600	101	0.10	1	2	3	4	5	6	7	8
B	10	1,580	120	0.25	9	10	11	12	13	14	15	16
C	25	2,560	104	0.43	17	18	19	20	21	22	23	24
D	52	4,000	102	0.65	25	26	27	28	29	30	31	32

* These groups constituted the series used at the onset of the study.
† The serial numbers of the rabbits are given.

weight (largest variation in group D was 90 Gm.) and age. The small rabbits came from the same litters. The values for the initial weight and the initial blood cholesterol level as tabulated are average figures. A comparison of the cholesterol values of the four groups shows that the variations were slight.

CLINICAL OBSERVATIONS

The rabbits' increase of weight is evident from the upper part of figure 1. No detailed analysis seems necessary. Up to the age of 12 months the weight of a healthy rabbit is a fairly reliable measure of its age; after that the gain in weight is rather moderate. Each weight curve is a composite value for all animals in a group. There were no appreciable differences between cholesterol-fed rabbits and controls, although the weight of the control animals was slightly lower than that of the cholesterol-fed rabbits. No weight differences were observed between the two sexes or breeds of rabbits.

The blood cholesterol values of the control animals (*a-d*) remained stable. Cholesterol-fed rabbits reacted with a gradual and almost steady increase. The two groups of younger animals (A and B) reacted alike and so did the two groups of older rabbits (C and D). The average maximum values for the four groups were 320, 322, 340 and 367 mg. per hundred cubic centimeters of blood; the terminal blood cholesterol levels were at 320, 320, 330 and 330 mg. per hundred cubic centimeters (fig. 1, lower part). Differences between sexes or breeds were not encountered.

POSTMORTEM OBSERVATIONS

A single rabbit (30) had grossly visible atherosclerosis: Multiple elevated pale yellow patches were scattered throughout the lower part of the thoracic and all of the abdominal aorta. The largest of the plaques was 6 mm. long and 3 mm. wide. The liver of this rabbit showed steatosis, not present in any of the other animals. The initial weight of the animal was 3,985 Gm.; eight weeks later the weight was 4,360 Gm. It was the highest weight reached by any of the rabbits at termination of the experiment. The blood cholesterol of this rabbit ascended from 104 to 340 mg. per hundred cubic centimeters in the course of the study.

Sections from various organs of all rabbits were stained by different methods. Microscopically, atherosclerotic alterations were found in 4 animals (30, 29, 28, 26), all of whom were 1 year old at the onset of the experiment. The animal with

grossly visible patches (30) showed histologically the highest degree of atherosclerosis: Cross sections of the aorta at various levels revealed an almost complete ring of foam cells piled in several layers beneath the endothelium and also thickening of the intima proper (fig. 2, upper part). Another rabbit (28) had patches

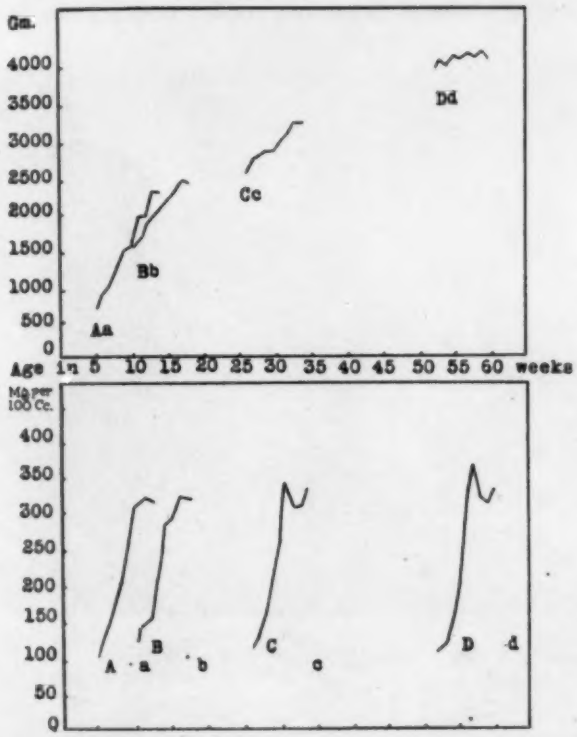

Fig. 1.—Upper part: Average weight (in grams) of the cholesterol-fed rabbits (*A-D*) and the controls (*a-d*).

Lower part: Average blood cholesterol values (in milligrams per hundred cubic centimeters) of cholesterol-fed rabbits (*A-D*) and of controls (*a-d*). The ages shown are the same for both charts.

TABLE 2.—*Data on Atherosclerotic Rabbits*

Rabbit	Weight, Gm.		Blood Cholesterol, Mg. per 100 Cc.			Days of Feeding
	Initial	Terminal	Initial	Maximal	Terminal	
30	3,985	4,360	104	350	340	60
29	4,040	4,200	95	340	320	60
28	4,020	4,310	112	290	300	45
26	3,950	3,970	92	280	280	30

of foam cells in the abdominal aorta only; these accumulations were less numerous and less extensive than those in the first animal (fig. 2, lower part). Finally, 2 more rabbits (29 and 26) had only isolated foam cells or small groups of up to six such cells lifting the endothelium (fig. 3). Data as to the weights and the blood cholesterol levels of these 4 rabbits are tabulated.

COMMENT

All 4 rabbits that reacted to cholesterol feeding with atherosclerotic manifestations belonged to the group of highest age and weight (D). The animal with the most severe alterations had the maximum terminal blood cholesterol value; the rabbit next in line as to degree

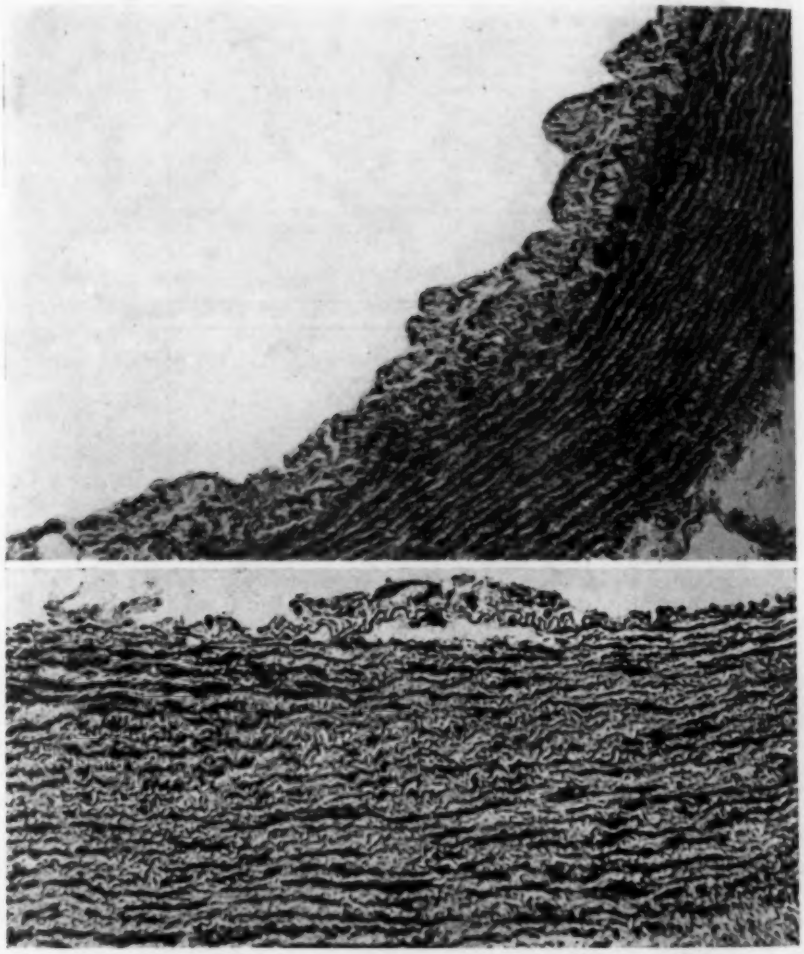

Fig. 2.—Upper part: Atherosclerosis after eight weeks of daily cholesterol feeding (0.1 Gm. per 600 Gm. of body weight); rabbit 30; fixation in solution of formaldehyde; rapid trichrome stain; × 100.

Lower part: Atherosclerosis after six weeks of feeding; rabbit 28; fixation in solution of formaldehyde; rapid trichrome stain; × 100.

of atherosclerosis was the one with the highest absolute value observed in the course of the study. While the blood cholesterol levels of the heavier animals were somewhat higher than those of the lighter

rabbits, the variation was too slight to explain the marked differences in anatomic findings. The differences were not larger than those of the initial blood cholesterol values. Also, while groups C and D had comparable blood levels, only animals of group D had atherosclerosis. Of 6 rabbits of group D, 4 responded to cholesterol feeding with

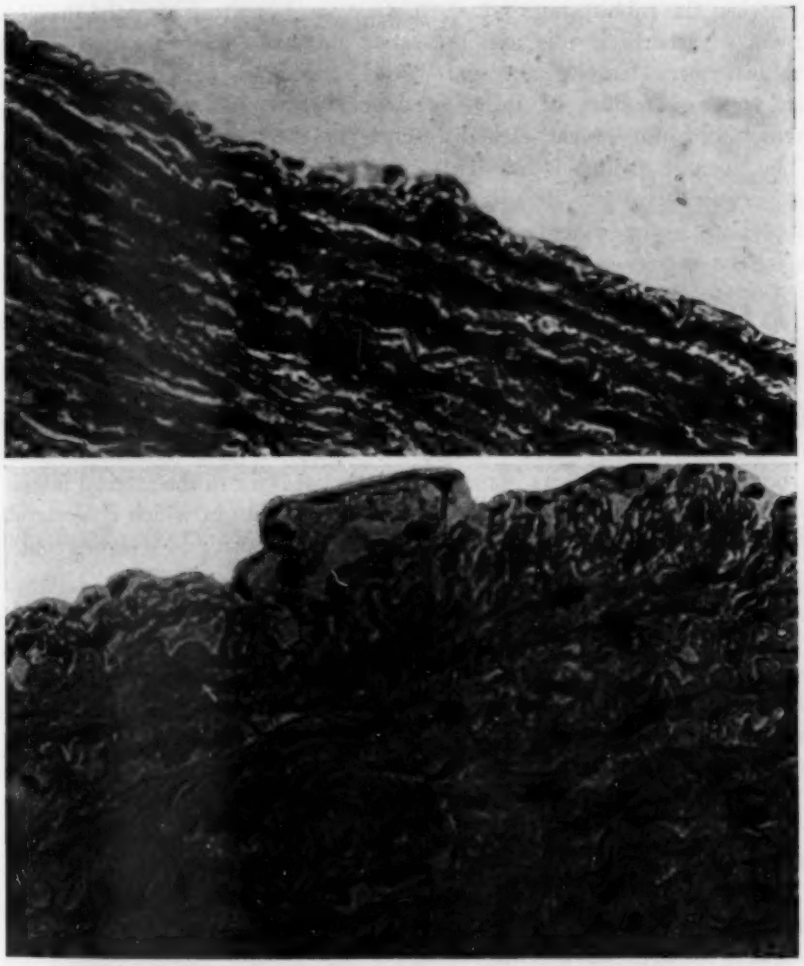

Fig. 3.—Upper part: Atherosclerosis after eight weeks of feeding; rabbit 29; fixation in solution of formaldehyde; rapid trichrome stain; × 475.
Lower part: Atherosclerosis after four weeks of feeding; rabbit 26; fixation in solution of formaldehyde; rapid trichrome stain; × 475.

vascular changes: 2 after sixty days, 1 each after forty-five and thirty days of feeding. The rabbit with alterations after a month of cholesterol diet had a blood cholesterol value of only 280 mg. per hundred cubic centimeters.

The study was planned so that the atherosclerotic manifestations might be detected as early as possible. Prolongation of the experiment would have been accompanied by aging of the animals. Even with our arrangement the youngest group (A) reached the weight and age of the next group (B).

Advanced age and high weight were the only points of difference between the rabbits responding to cholesterol feeding with the development of atherosclerosis and the other animals. The fact that 3 of 4 rabbits were females and only 1 a male does not seem important in view of results of previous experiments on much larger series which did not reveal any difference in the response of the sexes. The weight factor is obviously important for the development of experimental atherosclerosis of rabbits. This may apply to the age factor to some extent. By no means does it imply that atherosclerosis is a disease of old age. Experimental cholesterol-epinephrine hypertension develops more readily in rabbits after they cease to grow.[1] The individual ability to metabolize cholesterol varies: age seems to be one and weight is another of the factors responsible for such variations. The saturation point of blood cholesterol is higher in rabbits than in man. Owing to insufficient cholesterolysis, abnormal precipitation of cholesterol occurs. Atherosclerosis, then, is the result of local irritation arising from cholesterol deposits in the subendothelial layer of the arterial intima. Future efforts will be directed toward experiments in which cholesterolysis may be studied in rabbits of various age groups and weight groups.

SUMMARY

Under analogous experimental conditions, rabbits 1 year of age responded to cholesterol feeding with atherosclerotic alterations of the aorta, while rabbits 25, 10 and 5 weeks old did not. All rabbits, however, regardless of age, reacted with hypercholesteremia of almost equal degree.

Atherosclerosis of varying degree developed in 4 of the 6 rabbits that were 1 year old. The earliest manifestations were observed in a rabbit fed cholesterol for thirty days only.

It seems that the rabbit's age and weight constitute important factors in the development of experimental cholesterol atherosclerosis. Reports on experiments with rabbits should always include information concerning the age and the weight of animals.

1. Schmidtmann, M., and Hüttich, M.: Virchows Arch. f. path. Anat. **267**: 601, 1928.

LYMPHOSARCOMA OF THE LARYNX

Report of a Case

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LYMPHOSARCOMA of the larynx is rare. MacKenty [1] reported a case of a 45 year old man with a positive Wassermann test. There was some improvement with antisyphilitic therapy, but subsequently laryngectomy was performed. MacKenty stated that:

> Microscopic examination revealed marked edema and induration below the left vocal cord. The mucosa of the larynx was intact but very edematous, and in areas it showed cysts containing purulent fluid. Sections showed lymphosarcoma. Changes in the blood vessels suggesting syphilis and chronic inflammation were observed. The patient was still alive and well ten years later.

Another case was reported by Clerf [2] as follows:

> . . . A man aged 49 years was observed during July 1934. The voice was muffled, and there was a sensation of a lump in the throat for six months. An ulcerated mass was found involving the left half of the posterior surface of the epiglottis, extending along the left aryepiglottic fold. No lymph nodes were palpable. The appearances suggested carcinoma. The report of biopsy was lymphosarcoma. . . . A total of 1,930 [roentgen] units was given to each side of the neck. The lesion disappeared promptly, and the larynx appeared practically normal. There has been no recurrence, and the patient is well.

Leroux and Petit reviewed the French literature. They found reports of 26 cases of sarcoma of the larynx. Of these, 2 were cases of lymphosarcoma.

Only 15 cases of sarcoma of the larynx of all types were reported in the English literature from 1910 to 1940.[3] Additional reports have appeared recently.

Havens and Parkhill reviewed 1,100 cases of cancer of the larynx at the Mayo Clinic and found 8 cases of fibrosarcoma, 2 cases of chondrosarcoma and 1 case of rhabdomyosarcoma. However, there was not a single case of lymphosarcoma in this series.

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1. MacKenty, J. E.: Arch. Otolaryng. **20**:297, 1934.
2. Clerf, L. H.: Arch. Otolaryng. **44**:517, 1946.
3. Havens, F. Z., and Parkhill, E. M.: Arch. Otolaryng. **34**:1113, 1941.

In 196 cases of lymphosarcoma of all types, Sugerbaker and Craver [4] found no lymphosarcoma of the larynx. Cutler,[5] in reporting 30 cases of generalized lymphosarcoma with 13 autopsies, noted no involvement of the larynx. Hellwig [6] reported 202 cases of malignant lymphoma with 30 autopsies without any evidence of involvement of the larynx.

The case presented here is of interest because it is the only reported case with associated lymphatic leukemia. The incidence of lymphatic leukemia in cases of lymphosarcoma [4] is 6.6 per cent.

REPORT OF CASE

Mrs. M. F., aged 72, was first seen Dec. 3, 1946, at which time she was complaining of hoarseness of one month's duration. There had been no loss of weight and no other complaints. Biopsy of the larynx had been made on November 19. At the time of our first indirect laryngeal examination the appearance of the lesion was recorded as follows: ". . . there can be seen a verrucous lesion, probably beginning on the right false cord and lower ventricular cavity and extending onto the true vocal cord . . ." Grossly, the lesion appeared like carcinoma. There was bilateral soft cervical adenopathy, with one firmer, slightly fixed gland just lateral to the wing of the thyroid cartilage on the left side. Also present were soft, freely movable small nodes in both axillas and both inguinal regions. The rest of the examination gave essentially negative results. A roentgenogram of the chest showed nothing abnormal.

The biopsy of the larynx in sections stained with hematoxylin and eosin showed diffuse infiltration of the submucosa with small round cells containing hyperchromatic vesicular nuclei. There was infiltration of the walls of the blood vessels. Scattered mitotic figures were seen. December 13 a biopsy was made of an inguinal lymph node, which showed diffusely arranged round or oval cells with relatively large vesicular nuclei. There was no structural pattern characteristic of lymph nodes, and there were no giant cells, tubercles or granulomatous foci.

December 16, smears of the marrow taken by sternal puncture showed cells resembling lymphocytes with dense clumped chromatin in the nuclei and narrow margins of cytoplasm. These observations were consistent with chronic lymphatic leukemia. On December 16 the white cell count was 23,100. The differential count showed small lymphocytes 72, segmented polymorphonuclear leukocytes 21, stab forms 4, monocytes 2 and myelocytes 1 per cent. The lymphocytes were predominantly immature, and a few blasts were present. The red cell count was 3,810,000; the hemoglobin content, 12.79 Gm. or 76.2 per cent (photoelectric method); the color index, the reticulocyte percentage, 2.7. The coagulation time was three minutes fifteen seconds (venous); the bleeding time, left ear two and right ear three minutes. There was partial clot retraction in three hours; the mean corpuscular volume was 100 cubic microns (normal for adults, 82 to 92 cubic microns). The mean corpuscular hemoglobin was 33.4 micromicrograms (normal for adults, 29 to 31 micromicrograms). The hematocrit reading was 38 (normal for women, 42).

In spite of the fact that this was obviously a case of generalized lymphosarcoma with lymphatic leukemia, the only symptoms were

4. Sugerbaker, E. D., and Craver, L. F.: J. A. M. A. **115**:17 and 112, 1940.
5. Cutler, M.: Arch. Surg. **30**:405, 1935.
6. Hellwig, A.: Am. J. Clin. Path. **16**:564, 1946.

referable to the larynx. A total of 65,000 milligram hours of radium pack therapy was given to each side of the neck, with complete regression of the lesion and marked symptomatic relief. It is emphasized that the treatment was given as palliative and symptomatic. Because of the generalized nature of the disease and the associated lymphatic leukemia, the ultimate prognosis is poor.

SUMMARY

A review of the literature reveals reports of 4 cases of lymphosarcoma of the larynx. A case of generalized lymphosarcoma with localization in the larynx has been recorded in this paper. It is the only reported case of lymphosarcoma of the larynx with concomitant lymphatic leukemia. The lesion in the larynx showed complete regression and relief of symptoms following radium pack therapy.

Case Reports

PRIMARY PULMONARY ANTHRAX WITH SEPTICEMIA

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THIS report of an unusual case of pulmonary anthrax with septicemia is presented to call attention to a disease which has all too frequently been considered to be limited almost solely to the leather and hide industries and to frankly agricultural regions.

A review of the literature showed that up to recently pulmonary anthrax was extremely rare in the United States. However, a survey from 1939 to 1943 by the United States Public Health Service [1] showed numerous cases of internal anthrax. Over the last ten years there has been only one detailed report of a case of primary internal anthrax.[2] Anthrax septicemia following a cutaneous lesion is not uncommon. Lucchesi [3] reported a case of external and internal (pulmonary) anthrax with bacteremia, with recovery. Eurich [4] reported from Great Britain a series of 340 cases of anthrax, in 24 of which the disease was both pulmonary and intestinal.

REPORT OF A CASE

A 46 year old white man was hospitalized with a chief complaint of cough and dyspnea of three days' duration. He had been perfectly well until four days prior to admission, when he complained of a mild cough and a feeling of general malaise. Although he did not go to bed, he had fever and a headache, and an increasingly severe productive cough developed, accompanied by pain in the left side of the chest. Slight hemoptysis began before his symptoms became pronounced. The day before admission his temperature rose to 102 F., his sputum became blood streaked, and he began to breathe with more difficulty. Twelve hours later he suddenly became much worse. His breathing became labored and fast, he was cyanotic, and he began to bring up large amounts of bloody sputum. He became weak and semiconscious and then was brought to the hospital.

His past medical history was not significant.

Social History.—He had been discharged from the Army five months previously because of age. He had not been overseas. Just prior to his illness he

From the Department of Pathology, Temple University Medical School and Hospital, and the Medical Service of John B. Carson, M.D., Protestant Episcopal Hospital.

1. Smyth, H. F., and Higgins, W. D.: Am. J. Pub. Health **35**:850, 1945.
2. MacDonald, W. D.: New England J. Med. **226**:949, 1942.
3. Lucchesi, P. F.: Am. J. M. Sc. **183**:795, 1932.
4. Eurich, F. W.: Brit. M. J **2**:50, 1933

was a china and glassware salesman. Before the war he had been a rug merchant and he had recently been cleaning some new rugs which he had planned to sell.

Examination.—His temperature was 97 F.; pulse rate, 140; respiratory rate, 50; blood pressure, 90 systolic and 50 diastolic.

He was an extremely cyanotic, dyspneic, orthopneic, although well nourished, man of 46, who coughed continually. From the corner of his mouth ran a brownish red sputum. He was sweating profusely. His skin was cold and clammy. He appeared moribund. The head was normal except for the severe cyanosis. The pupils were widely dilated and did not react to light. There was no nasal discharge or obstruction. The mouth disclosed a dry and coated tongue. The pharynx was not inflamed. The neck showed no lymphadenopathy. The veins were not distended. The trachea was in the midline. The thyroid gland was not enlarged. The chest showed a lag on the left, and there was dulness to percussion over the left base and in the left axilla. Over this area there was bronchial breathing with many rales. For the remainder, the lung fields were clear. The heart was not enlarged. The sounds were regular, rapid and strong. The aortic second sound was greater than the pulmonic second sound. There were no murmurs. The pulse was rapid, weak and thready. The liver and the spleen were not felt. The extremities were cyanotic and cold. No edema, clubbing or purpura was present.

The patient was put in an oxygen tent and died two hours after admission. No laboratory work was done.

Necropsy (twenty hours after death).—The body was that of a well developed and well nourished 46 year old white man. There was marked generalized post-mortem lividity. There were no scars, abrasions, palpable lymph nodes or evidence of cutaneous areas of infection.

The left pleural cavity contained about a liter of clear yellow fluid; the right, approximately 500 cc. There were numerous enlarged hemorrhagic black mediastinal and hilar lymph nodes, measuring up to 3 cm. in diameter. The pericardium contained about 75 cc. of clear fluid.

The heart weighed 340 Gm. and appeared normal.

The right and left lungs weighed 540 and 770 Gm., respectively. The right lung was reddish gray, and its pleural surface was smooth and moist. The parenchyma was deep purplish red and poorly aerated. About the hilus and extending upward toward the apex in the mediastinum was a mass of lymph nodes, which were intensely hemorrhagic. The nodes around the hilus appeared to press on and compress the lower branch of the pulmonary artery, practically occluding the lumen. Many of the nodes looked like blood clots, while others showed traces of grayish lymphoid tissue. The left lung was heavy, and the lower lobe was enlarged and firm. The pleural surface was smooth and deep reddish purple. The entire lobe had a gelatinous and homogeneous blackish red appearance. It contained no air and was friable. The upper lobe was congested and edematous.

The spleen weighed 60 Gm. The capsule was gray and wrinkled. The parenchyma was pinkish gray, congested and mushy.

The liver weighed 1,500 Gm. The capsular surface was reddish brown and showed small circumscribed bluish black areas beneath the capsule. These measured approximately 1 cm. in diameter and proved to be small cavities which contained dark clotted blood. The parenchyma was smooth and brownish red.

Both adrenal glands were small and thin, owing to an exceptionally narrow cortex. They were pale in color and well preserved.

The right kidney weighed 170 Gm. and the left 150 Gm. The cut surfaces were plum colored, owing to marked congestion. The cortex was wide and well defined. The ureters, the bladder and the prostate were normal.

The external surface of the bowel was smooth and glistening. The gastric rugae were prominent, and numerous small superficial ulcers were noted. These were confined to the lower portion of the body and pyloric vestibule. They were most numerous along the greater curvature. The lesions measured from 0.5 to 1.5 cm. in diameter. Some were flat erythematous plaques; others showed shallow central ulcerated necrotic centers, and still others showed rolled indurated edges with fairly deep ulcerated necrotic centers. All of the lesions were covered with a thick clear gelatinous exudate. Several similar lesions were found in the duodenum, jejunum and ileum. None were found in the large bowel.

The pancreas appeared normal. The brain was not examined.

Microscopic Observations.—The outstanding histologic changes were the marked frank hemorrhage, congestion and almost total absence of polymorphonuclear cells, even in the areas of liquefaction necrosis. The preponderance of mononuclear phagocytes laden with hemosiderin in all areas of infection was noteworthy. Contrary to the recognized pathologic descriptions, the blood vessels in this case were not thrombosed. Even the smallest branches were normal. No bacilli were demonstrated in the vessels in sections stained by Goodpasture's technic.

The lower part of the left lung showed a thickened pleura infiltrated with mononuclears. The bronchi were filled with detritus; the mucosa had sloughed away partially to completely. The alveolar walls were thickened, owing to capillary dilatation. The spaces were filled with blood. There was secondary atelectasis, with practically no inflammatory response. Hemosiderin and "heart failure" cells were innumerable. The right lung showed hemorrhage in the alveolar spaces, but the alveolar walls and bronchi appeared much less affected.

The aorta showed several early atheromas. The heart revealed severe myocardial degeneration and marked congestion but no hemorrhage.

The liver contained several cavernous hemangiomas and was congested throughout, with marked fatty changes.

The renal glomeruli were enlarged, owing to congestion of capillaries. There was marked tubular degeneration, and hemosiderin-laden phagocytic mononuclears were found everywhere.

Each adrenal gland showed a narrow cortex and some autolysis.

The spleen displayed complete destruction of the internal structure. There was hemorrhage throughout. Again one was impressed by hemosiderin-laden macrophages.

The stomach revealed congestion of the vessels, hemorrhage, necrosis and edema, with ulceration of the mucosa. Large rod-shaped bacilli were numerous in the ulcer craters and invaded the mucosa in great numbers, extending down to but not into the submucosa. Hemosiderin-laden macrophages were numerous.

The small intestine showed a picture practically identical with that in the stomach except that the hemorrhage was confined to the tips of the villi. Bacilli were countless around the ulcerated areas.

The pancreas showed only acute congestion and granular degeneration.

All of the hilar lymph nodes examined showed massive hemorrhage—in some cases, involving all of the node. There was complete loss of the internal structure, and in some areas, necrotic liquefaction. The nodes were filled with macrophages. The vessels were dilated and congested, but no bacilli were seen.

Bacteriologic Observations.—Aerobic and anaerobic cultures of material from the liver, the mediastinal lymph nodes and the larynx presented a moderate number

of colonies of anthrax bacilli. Staphylococci and hemolytic streptococci were isolated in small numbers from the larynx and the liver.

COMMENT

Human anthrax is not rare in the United States. The recent public health survey from 1939 to 1943 shows a 16 per cent increase of cases of anthrax for the period. The infection occurred in people who had no occupational contact with infected material. One patient was a football player (soil?). Several patients were children; one of these, 10 years old, was resident in a mining location in a state where animal anthrax had been unknown for ten years; this child died of a pulmonary and blood stream infection. Other patients were housewives. Some of these had been gardening; others contracted the disease from tooth brushes, shaving brushes and a fur coat. Many of these cases were the fatal pneumonic type.

No longer can physicians think of anthrax as a disease limited to a few industrial and agricultural areas. While Pennsylvania has had a large number of cases of anthrax annually because of its tanneries and woolen mills, the present case is a good example to prove that anthrax may occur anywhere.

The unusual picture which this case presented in the clinical findings, in the gross pathologic findings and in the histologic observations seems to warrant this report.

ACINOUS CELL CARCINOMA OF THE PANCREAS WITH EXTENSIVE FAT NECROSIS

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IN CASES of pancreatic carcinoma it is not uncommon to find small foci of fat necrosis in the pancreas or even in the neighboring peritoneum, omentum or mesentery. Fat necrosis around distant metastases has also been described.[1] The presence, however, of areas of fat necrosis in the subcutaneous tissue, the heart, the renal capsule and other localities devoid of metastases is exceptional. To my knowledge, only 1 case of pancreatic carcinoma accompanied by such widespread and distant fat necrosis has been reported in the literature.[2] The following report concerns a second case with similar features.

REPORT OF A CASE

A white man 56 years of age was admitted to the Hôtel-Dieu Hospital, Quebec, Canada, June 24, 1946, complaining of severe pain in both feet and hands. Dr. J. B. John kindly furnished the clinical notes.

The family and the past history were noncontributory.

Two weeks prior to admission the patient suddenly began to suffer from sharp, persistent pains in both heels. There was some local tenderness but no swelling. Later the middle finger of the right hand also became persistently painful, and for a few days the knuckle of the same finger was slightly enlarged and red. Pains also appeared in the left hand and in both elbow regions. These pains were accompanied by insomnia, fever and spells of profuse sweating. During the last two months there was a loss of 35 pounds (about 16 Kg.). The patient complained also of anorexia and periodical digestive malaise. His temperature was 101.1 F.; the pulse rate, 88; the respiratory rate, 24; the blood pressure, 110 systolic and 70 diastolic. The patient was emaciated and definitely underweight. He appeared to be acutely ill and in severe discomfort. The skin was sallow with a tint that suggested jaundice. The conjunctivas were pale. Examination of the heart, lungs and abdomen failed to show any deviation from normal. The prostate was small and presented a smooth, regular surface on rectal examination. Several areas of tenderness were found in the vicinity of the joints on both arms and legs. There were no local swellings and no limitation of joint movements.

On admission the hemoglobin content of the blood was 75 per cent; the erythrocyte count 3,350,000 per cubic millimeter, with a mean cell diameter of 7.4 microns and a color index of 1.11. The leukocyte count was 5,428 per cubic millimeter; the differential count showed segmented neutrophils 50, stab neutrophils 21, eosinophils 8, lymphocytes 19 and monocytes 2 per cent. Urinalysis gave negative

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From the Institute of Pathology, Laval University, and the Hôtel-Dieu Hospital.

1. Hegler, C., and Wohlwill, F.: Virchows Arch. f. path. Anat. **274**:784, 1930.

2. Titone, M.: Virchows Arch. f. path. Anat. **277**:416, 1936.

results. The sedimentation rate was 90 mm. after one hour and 122 mm. after two hours, and the blood urea was 33 mg. per hundred cubic centimeters. Blood cultures remained sterile, and serologic tests for syphilis (Klein), Eberthella typhi, Salmonella paratyphi, Salmonella schottmülleri and Brucella abortus were negative.

Fourteen days after admission, July 8, a mass the size of a hen's egg appeared in the subcutaneous tissue over the anterior part of the crest of the right ilium; this mass was definitely fluctuant and tender, and the overlying skin was slightly congested. Two days later a similar but smaller nodule developed in the hypothenar region of the right hand. In the following days other nodules of various sizes appeared in the subcutaneous tissue of the back and of the hypothenar region of the left hand, of the left elbow region and at the base of the big toe of the left foot.

The sharp pains in both arms and legs persisted throughout the patient's hospitalization; they increased in severity and were little relieved by sedatives. The patient took little or no food and continued to lose weight rapidly. His temperature remained high, some days reaching 103 F.

Roentgenograms were made of the heart, aorta, lungs, thoracic wall, stomach, intestine, gallbladder and spine and of the bones and joints of the sacroiliac regions. The only abnormal findings were a moderate distention of all segments of the duodenum and a nonopacified gallbladder fourteen hours after ingestion of Priodax.

On July 18 a few cubic centimeters of brownish material was obtained by puncture of the mass in the right hypothenar region. Microscopically, this material was made up of necrotic tissue debris with only a few inflammatory, generally polymorphonuclear, cells. Bacterial examination gave negative results.

In August recurrent nausea and vomiting appeared. The liver became enlarged, extended below the right costal margin and on palpation showed a hard and nodular surface. The lower extremities became edematous. The patient died on August 18, forty-six days after admission.

Autopsy (three hours after death).—The body was that of an emaciated adult white man. The skin and conjunctivas were slightly icteric. Marked edema was present in the feet and malleolar regions. There was a noticeable swelling of the first metatarsophalangeal region of the left foot. The epidermis was intact, but in the subcutaneous layers the tissues lost their normal luster, were gray-yellowish and had the general aspect and consistence of putty. Toward the plantar region the tissues had broken down; there was a cystic cavity containing approximately 1 cc. of thick, granulated, brownish, liquid material. The joint was normal. The soft tissues of both heels showed the same necrotic transformation with many isolated and small liquefied foci. In these regions the skin was ulcerated. Similar areas of necrosis were found in the adipose tissue overlying the crest of the right ilium, in the soft tissues of both hypothenar regions, in the thenar region of the right hand, in the dorsal region of the left hand and on the external and internal aspects of both elbows. These regions were definitely swollen and covered by normal-looking skin.

The smoothly lined pleural cavities contained approximately equal amounts of clear yellow fluid: the right, 870 cc.; the left, 850 cc. In the pericardium 40 cc. of similar fluid was found. The peritoneal surfaces were dry but showed disseminated, patchy, gray-yellowish areas, waxlike in appearance and extending deeply in the retroperitoneal fat layers. The mesentery, the omentum and the intestinal serosa contained numerous irregular nodules of similar aspect.

The esophagus, the stomach and the intestine revealed no mucosal abnormalities. The tail of the pancreas was enlarged by a firm, spherical mass 5 cm. in diameter. On section this mass did not have definite boundaries and showed the same

finely lobulated structure, texture and gray-pink color as the neighboring pancreatic parenchyma. Around this mass and in the head and body of the pancreas small waxlike areas were present. The spleen weighed 200 Gm. and was normal in shape and in color; in the lower half of the internal aspect the capsule was thickened and adhered to the pancreatic tumor. The liver weighed 3,300 Gm., was increased in size and contained numerous round or oval-shaped gray-pink nodules. The largest nodule, 12 cm. in diameter, occupied the posterior region of the right lobe, had a small necrotic center and was compressing the cystic duct. The gallbladder was distended and contained a rather large quantity of clear, yellow and very fluid bile. The gross aspect of the adrenal glands was normal. Each kidney weighed 150 Gm. and was slightly congested. The ureters, the urinary bladder, the prostate and the testes were not remarkable. The fat tissue surrounding each kidney and pelvis, the bladder and the prostate showed many waxlike areas similar to those seen in the mesentery and elsewhere.

The heart weighed 310 Gm.; the endocardial surfaces, the valves and the myocardium showed no gross abnormalities; in the subepicardial fat tissue of the right and posterior aspects of the right auricle, of the right auriculoventricular groove and around the descending right coronary artery, there were many gray, cheeselike, dry, irregular areas. In all pulmonary lobes crepitation was diminished; sections revealed deep red parenchyma oozing some serosanguinous fluid; a few millimeters under the left lower lobe there was a small calcified nodule of pea size. The trachea and bronchi were congested.

The aorta was not remarkable. The inferior vena cava was distended and its lumen was filled with red thrombotic material adherent to the walls and extending from the subhepatic veins to the common iliac veins.

Chemical analysis of liquid material collected from the right hypothenar region (Dr. H. Marcoux) showed presence of neutral fats and of cholesterol in large quantities.

Microscopic Examination.—The tumor of the tail of the pancreas was made up of medium size monomorphous polygonal cells with abundant homogeneous and basophilic cytoplasm and either round or slightly indented nuclei, rich in chromatin and containing one or two prominent nucleoli. These cells were arranged in thin trabeculae, separated by strands of collagen and capillaries, and here and there were definitely oriented around minute lumens, forming thus acinous structures. Many of the cells contained highly refractile uniform granules, staining deeply with acid dyes. These granules were generally scattered throughout the cytoplasm, but in the cells bordering a lumen they formed dense clusters in the apical end and had all the characteristics of zymogen granules. Mitotic figures were exceptional. The tumor was divided into angular lobules by connective tissue septums containing blood and lymphatic vessels and small nerves. Under low power the general aspect had a striking resemblance to normal pancreatic tissue. No centroacinous cells, tubular structures or islet formations were seen. The outlines of the tumor were irregular, and the neighboring pancreatic parenchyma was distinctly infiltrated by lobulated tumor tissue. The histologic characters of the tumor were therefore those of a highly differentiated acinous cell adenocarcinoma.

Around the tumor and in the subcapsular and interlobular fat of the body and head of the pancreas, many small areas of typical fat necrosis were present.

The hepatic parenchyma showed marked stasis and a slight degree of fatty metamorphosis, but the largest part of the sections examined was made up of metastatic nodules having the same general cell pattern as the pancreatic tumor.

Most of the cells contained numerous refractile granules with all the characteristics of zymogen granules. Very small areas of the nodules were necrotic.

Most of the capillaries of the kidneys were distended by red blood cells. In a few spots the capsule was moderately thickened and a small triangular zone of

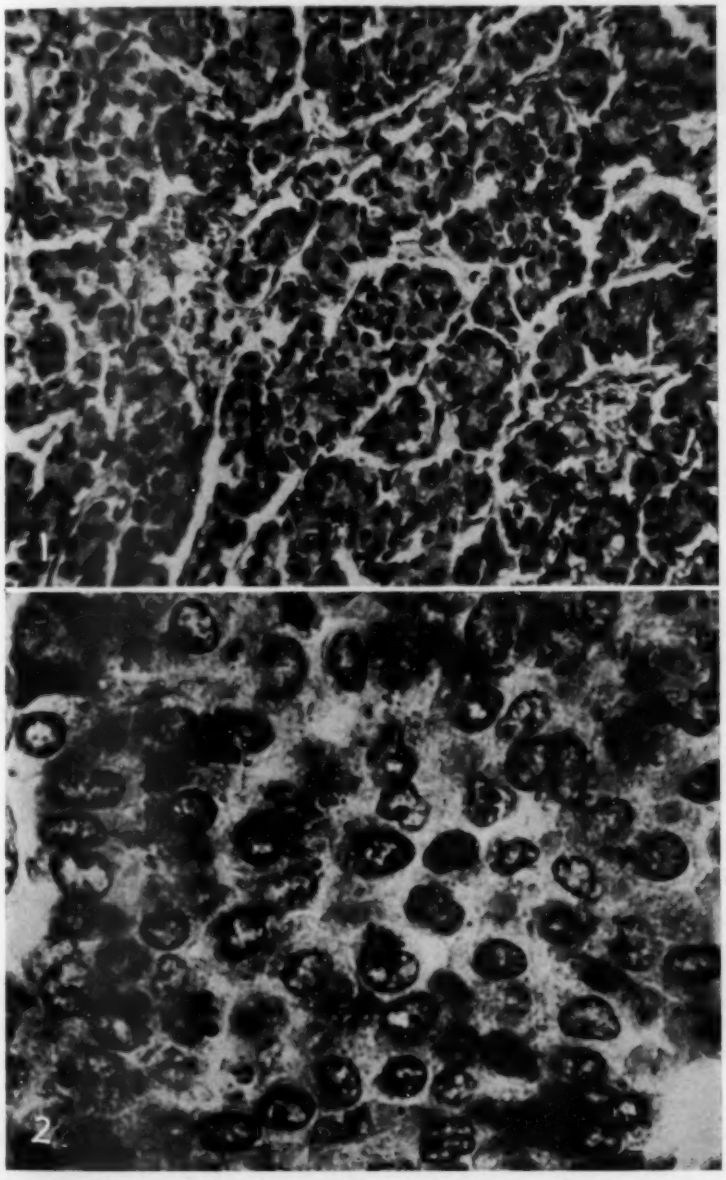

Fig. 1.—Section of the pancreatic carcinoma illustrating the resemblance to normal pancreas. Hemalum, phloxine and saffron; × 230.

Fig. 2.—Section of tumor tissue showing the presence of zymogen granules. Mallory's phosphotungstic acid-hematoxylin; × 900.

the subjacent parenchyma showed a moderate lymphocytic infiltrate, some tubular atrophy and a few sclerotic glomeruli. With sudan III and IV, small fat droplets could be seen in the epithelial cells of many of the distal convoluted tubules.

Sections of the mesentery, of the omentum and of the perirenal and peripelvic fat showed numerous foci of typical fat necrosis. These foci were made of cloudy fat cells devoid of nuclei with here and there small clusters of radiating crystal-like rods. Many of these foci were small, and in their center a small blood vessel with an entirely necrotic wall could be seen. The lumen of this vessel was either free or contained a small fibrinous clot. The area of necrosis was equally distributed around this vessel and appeared clearly to be oriented around it. Other much larger foci contained cystic spaces filled with necrotic cellular debris and amorphous material. Here and there thin peripheral zones of round cells were present. In none of these foci, nor in their vicinity, were any metastatic cells seen.

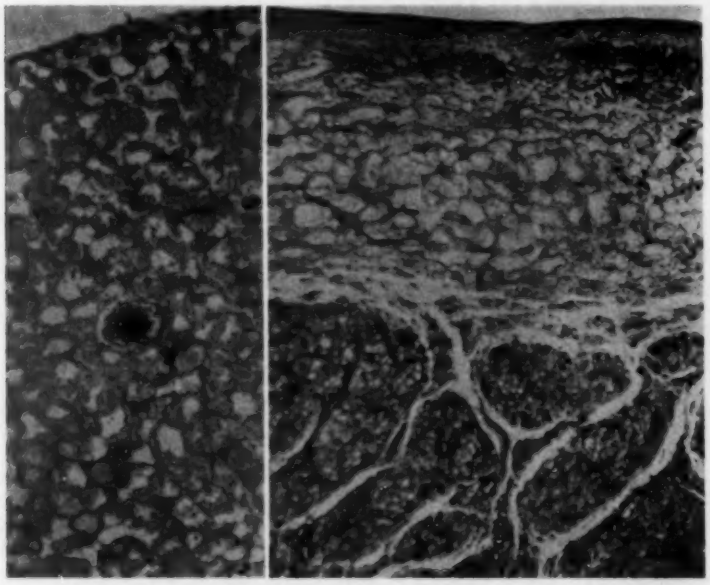

Fig. 3.—Perirenal fat lobule which has undergone fat necrosis and is centered by a small necrotic blood vessel. Hemalum, phloxine and saffron; × 72.

Fig. 4.—Section of the right auricle showing necrosis of the fat layer of the pericardium. Hemalum, phloxine and saffron; × 72.

The lumen of the inferior vena cava was occluded by a fibrinohemorrhagic thrombus without any signs of organization or fibroblastic activity. In the center of the thrombus a few linear structures were suggestive of necrotic remnants of preexisting cellular formations. In the intima of the vessels there were in one spot a few rather clear epithelial cells oriented around a small lumen. These cells, evidently undergoing degeneration, were taken as metastatic.

The myocardium and the coronary arteries showed no microscopic abnormalities. The subepicardial fat tissue, in sections of the right auricle and of the left auriculoventricular groove, contained diffuse and large areas of fat necrosis, partially surrounded by a small number of round cells. All the cells of these areas were more or less cloudy, and their nuclei had disappeared. The walls of the small blood vessels of these areas were also necrotic.

The subcutaneous nodules were made up of swollen subcutaneous fat tissue in different stages of necrosis. In some spots the cell outlines were still vaguely recognizable, but generally the tissue was replaced by foci of anhistic material, irregularly stained by hematein. These foci contained large clefts and cystic spaces where the material had evidently broken down and become liquefied. The subcutaneous connective tissue septums throughout the lesions and the neighboring aponeuroses and derma showed only a slight round cell infiltrate. In sections taken from the left heel, a few small purulent foci and a limited number of gram-positive cocci were also present. In these sections the overlying skin was ulcerated. Nowhere were any metastatic cells found.

COMMENT

From the pathologic observations it seems reasonable to conclude on morphologic grounds alone that in the present case the carcinoma of the pancreas and the hepatic metastases were functional. The tumor tissue was clearly of the acinous cell type and contained numerous granules, evidently zymogen granules. Functional activity of acinous cell carcinoma is not unlikely. Sugiura and associates [3] compared the amylolytic action on starch, the proteolytic action on casein and peptone and the lipolytic action on several esters of extracts of a parenchymatous adenocarcinoma of the pancreas with those of three normal pancreases and found no significant differences. Comfort and associates [4] reported a case of acinous cell carcinoma of the pancreas in which values for lipolytic and amylolytic activity in the serum and ascitic fluid were exceedingly high. These authors came to the conclusion that these high values in all probability were due to functional activity of the tumor. In the case presented here no enzyme studies were made. The extensive fat necrosis is in favor of a high lipolytic activity of the blood serum. The necrotic areas did not contain any tumor cells and appeared to have developed, in general, perivascularly. Many of these areas were plainly centered by a small necrotic blood vessel. The absence of centroacinous cells and tubular structures in the tumor tissue is also in support of the conclusion that the cellular secretion is taken up by the blood stream. This case is reported as another example of how neoplasms may carry on some of the functions of their parent cells.

The course of the illness was accelerated by thrombosis of the inferior vena cava. The association of venous thrombosis, often multiple, with carcinoma of the pancreas is frequently encountered.[5]

SUMMARY

A case of highly differentiated acinous cell carcinoma of the tail of the pancreas with hepatic metastases is reported. Many of the tumor cells contained zymogen granules. Widespread fat necrosis of the subcutaneous tissue, the heart, the peritoneum, the omentum, the mesentery, the perirenal and peripelvic fat and other localities was present. These findings are in support of the conclusion that the tumor was functional.

3. Sugiura, K.; Pack, G. T., and Stewart, F. W.: Am. J. Cancer **26**:351, 1936.

4. Comfort, M. W.; Butt, H. R.; Baggenstoss, A. H.; Osterburg, A. E., and Priestley, J. F.: Ann. Int. Med. **19**:808, 1943.

5. Sproul, E. E.: Am. J. Cancer **34**:566, 1938.

RUPTURE OF THE HEART FROM BLAST INJURY

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THE USE of powerful explosives during World War II has served to focus the attention of the medical and surgical professions on injuries resulting from their use. The syndrome of blast injury has become well recognized, and injuries of the brain, the lungs, the cardiovascular system and the intestines have been described.

Many of the persons so injured have been battlefield casualties, and opportunity for postmortem examination has not been afforded. Conjecture only is possible in considering the cause of death in these cases. However, rather unusual pathologic conditions were found at postmortem examination in a soldier who had suffered a severe blast injury. It may be that the acute cardiac tamponade which he suffered may not be as rare as is commonly thought and that more such injuries might have been found if opportunity for postmortem investigation had been afforded. Acute tamponade of the heart in civilian practice is most commonly the result of stab or gunshot wounds.

Recorded cases of acute tamponade of the heart from blast are infrequent. The patient whose history is being reported was a 19 year old white soldier, a member of a blasting and drilling crew, who was accidentally injured in a premature explosion of dynamite while he was working directly over a drill hole in which the explosive had been placed. Death apparently occurred almost immediately.

Postmortem examination revealed multiple cutaneous injuries. Several of the teeth of the upper and lower jaws were fractured at the roots.

The left pleural cavity contained about 200 cc. and the right about 60 cc. of sanguinous fluid. The lungs each weighed 675 Gm. The pleural surfaces of the lungs were smooth, moist and glistening, but the lungs were deep red, with decreased crepitation. The cut surfaces were deep red, and a sanguinous fluid was seen to ooze from them when they were cut. The bronchi were deep red and contained sanguinous fluid.

The pericardial sac was tense and blue-black, with the color of the enclosed blood showing through it. About 700 cc. of liquid and coagulated blood was found within the sac. The heart weighed 240 Gm. and measured 10.5 by 9.5 by 7 cm. Three rents were found in the left ventricle (figure) measuring 3, 2 and 1 cm. in length. The largest was located 1 cm. from the apex and 3 cm. from the anterior interventricular groove. The laceration measuring 2 cm. was adjacent to the left coronary artery at an angle of about 20 degrees, while the smallest laceration was found 1 cm. inferior to the base and 0.5 cm. distal to, and parallel with, the laceration measuring 2 cm. The lacerations measuring 3 and 1 cm. communicated with the left ventricle, but the tear measuring 2 cm. did not extend through the entire thickness of the myocardium. The leaflets of the valves were

smooth, moist and glistening. Abnormalities of the coronary arteries were not found. The left ventricular wall was 1.5 cm. in thickness and the right 0.7 cm.

A moderate injection of the mucosa of the stomach was present, and the duodenum was deep reddish purple, showing marked congestion. Several deep reddish black areas measuring up to 1 cm. in maximum diameter were found in the wall of the small intestine. A perforation about 0.5 cm. in diameter was present in the jejunum about 4 meters distal to the ligament of Treitz. A small

A photograph of the heart revealing the three lacerations in the myocardium of the left ventricle.

hemorrhagic area was found in the cecum. The remainder of the postmortem examination did not reveal anything unusual.

Death was obviously caused instantaneously by rupture of the left ventricle with the resultant hemopericardium and acute cardiac tamponade. This injury was the direct result of the blast as proved by the facts that there was no penetrating wound of the chest and the pericardial sac was intact.

HELMINTHIC INFECTION OF THE WALL OF THE GALLBLADDER

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WHEREAS the finding of worms in the lumen of the gallbladder is reported from time to time, helminthic infection of the wall of the gallbladder seems to be rare, especially in surgical material. In the textbooks of Kaufmann,[1] Faust,[2] Walters and Snell [3] and in Hanser's [4] article in the Henke-Lubarsch *Handbuch* this localization of the worms is not mentioned, and only the occurrence of Ascaris, Opisthorchis felineus, Clonorchis sinensis and Fasciola hepatica in the lumens of the bile ducts or that of the gallbladder is discussed. Stein [5] found eggs of Schistosoma haematobium in the mucosa and submuscularis of the gallbladder of a Bantu man, who was killed in an accident. The eggs had provoked almost no reaction. There were only a few eosinophilic leukocytes and round cells. Stein [5] cited Hashim [6] as having reported 6 cases of bilharziasis of the gallbladder and Makar [7] as reporting the observation of bilharzia in a gallbladder removed surgically—according to Stein,[5] the first case in which this diagnosis was made in connection with the living.

In the case to be reported a worm was found in the wall of a gallbladder which had been removed for cholelithiasis and probable cholecystitis.

REPORT OF A CASE

A 28 year old woman, a native of Suriname, Netherland West Indies, was admitted with the history that since two days prior to hospitalization she had been suffering from violent pains in the right upper quadrant of the abdomen; the pain irradiated to the back and the right scapula. She had vomited several times. There had been no diarrhea. A month prior to this she had had an attack of the same nature but not so violent. Two years before admission she had been operated on for acute appendicitis, and three years before, for a right inguinal

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From the Public Health Service.

1. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie für Studierende und Aerzte, ed. 10, Berlin, Walter de Gruyer & Co., 1931, vol. 1, p. 954.
2. Faust, F. C.: Human Helminthology, ed. 2, Philadelphia, Lea & Febiger, 1939, pp. 174, 221, 231 and 476.
3. Walters, W., and Snell, A. M.: Diseases of the Gallbladder and Bile Ducts, Philadelphia, W. B. Saunders Company, 1940, p. 173.
4. Hanser, R.: Die Gallenblase, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 5, pt. 2, pp. 853-860.
5. Stein, H. B.: South African M. J. **12**:297, 1938.
6. Hashim, M.: J. Egyptian M. A. **14**:461, 1931; cited by Stein.[5]
7. Makar, N.: J. Egyptian M. A. **20**:512, 1937; cited by Stein.[5]

hernia. Ten years before, microfilarias had been found in her blood. She had never had malaria or bilharziasis.

Clinical, chemical and roentgen examinations gave the typical findings of cholelithiasis. No worm eggs, amebas, cysts or larvae of Strongyloides stercoralis

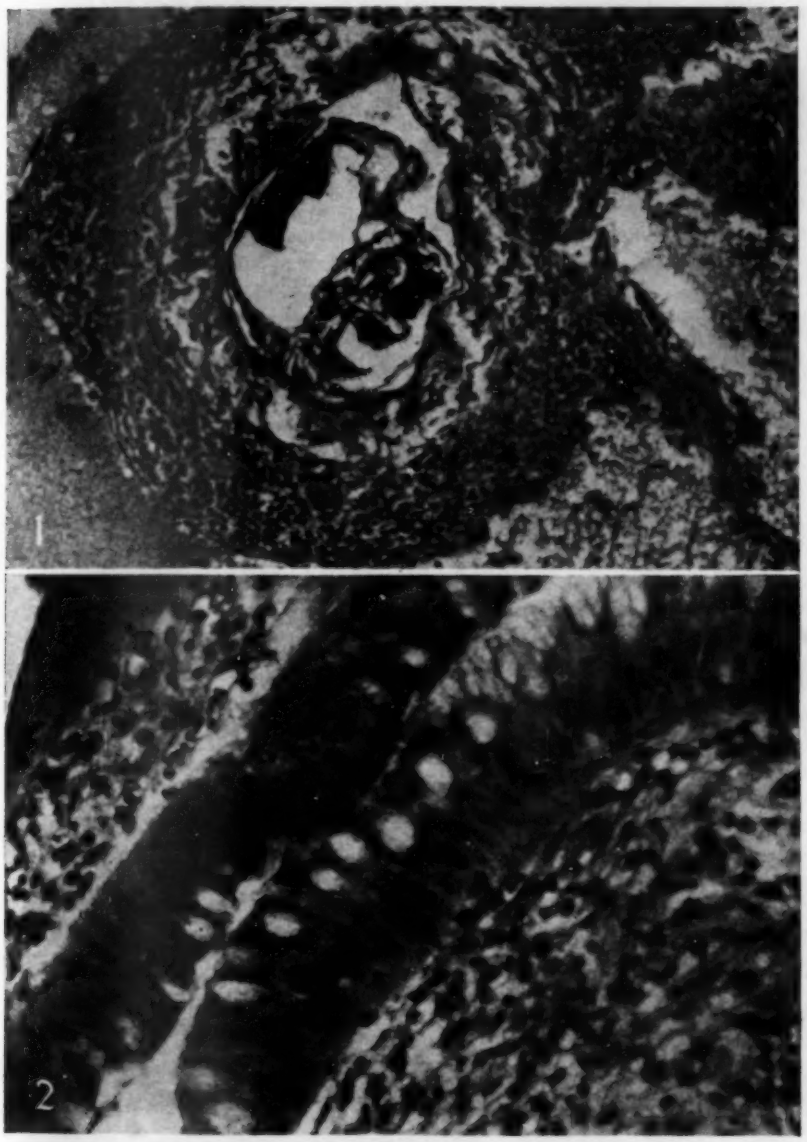

Fig. 1.—Cross section of the necrotic worm, which is surrounded by granulation tissue as it lies in a lymph vessel; × 190.

Fig. 2.—Goblet cells in the epithelium of the gallbladder; × 380.

were found in the feces. Eosinophils constituted 21 per cent of the leukocyte count of the blood. No microfilarias were found in the blood taken at night.

Cholecystectomy was performed. The postoperative course was uneventful, and the patient left the hospital fifteen days after the operation. Three months later examination of the blood showed the presence of microfilarias.

The gallbladder was distended; the wall was slightly thickened. The viscus contained about a hundred small faceted yellowish stones. The mucous membrane was intact.

Microscopic Examination.—Immediately after its removal from the body the gallbladder was opened and fixed in the Bouin fluid–mercury bichloride mixture.[7a] The sections were stained with hematoxylin–azophloxine [7b] and with hematoxylin-mucicarmine.[7c]

The surface epithelium was everywhere intact; the predominant high columnar cells showed a certain pleomorphism. Many cells had homogenous protoplasm whereas others resembled the surface epithelium of the stomach. There were also many typical goblet cells, containing distinct premucin granules. With the mucicarmine stain, cells without mucus, cells with only a little mucicarminophil substance directly above the nucleus and in the apex of the cell, cells of which the whole supranuclear region was filled with mucicarminophil substance and typical goblet cells could be demonstrated. Only the goblet cells contained premucin granules. There were many Rokitansky-Aschoff sinuses and also small glands, which normally occur only in the neck of the gallbladder but were found here also near the fundus. They opened into the Rokitansky-Aschoff sinuses. Also a few typical argentaffine cells were observed.

The epithelium, especially that in the sinuses and in the glands, but also the surface epithelium, showed marked mitotic activity. Sometimes 7 or 10 mitoses could be counted in the field of a 4 mm. objective and a × 7.5 eye piece.

The muscular coat of the gallbladder was hypertrophic: the subserosa was edematous and contained markedly dilated lymph vessels, which in some places formed a kind of cavernous tissue.

In both the mucosa and the subserosa, especially in the latter, numerous eosinophilic leukocytes were found. This, together with the conspicuous dilatation of the subserosal lymph vessels made us suspect the presence of a worm, as the microscopic picture resembled that found in some cases of filariasis.

Additional sections revealed the presence of a necrotic worm in the subserosa. It was recognizable by its cuticula. In one place the probable localization of the worm in a lymph vessel could be ascertained. The greatest part of the worm was surrounded by a zone of necrosis which was walled off by elongated epithelioid cells, often containing phagocytosed material. The layer of epithelioid cells was in turn surrounded by a granulation tissue consisting of a few plasma cells, large histiocytes, often containing acidophilic material, large fibrocytes and innumerable eosinophilic leukocytes. In one section giant cells were in direct contact with the cuticula of the worm. In the epithelioid cells and histiocytes a few mitoses were observed.

The organs of the worm could not be clearly recognized. It did not contain pigment. Sometimes a red-staining substance seemed to radiate from the cuticula, resembling the clubs of Actinomyces.

COMMENT

As the worm was necrotic, it was difficult to classify it. Though the patient came from Suriname, where bilharziasis is frequent, infection

7a. Hartz, P. H., and Hugenholtz, M. J.: Am. J. Clin. Path. **12**:523, 1942.

7b. Goldner, J.: Am. J. Path. **14**:237, 1938.

7c. Cowdry, E. V.: Microscopic Technique in Biology and Medicine, Baltimore, Williams & Wilkins Company, 1943, p. 126.

with Schistosoma was not probable. No eggs were found in the feces or in the wall of the gallbladder. The worm did not contain pigment and was probably lying in a lymph vessel, which certainly speaks against Schistosoma. There were not and had never been symptoms of bilharziasis. Therefore bilharziasis or schistosomiasis must be considered as improbable.

It must be considered possible that a larva of Ascaris might by accident have lodged in the wall of the gallbladder. However, the worm was too large for a larval ascarid, and an adult ascarid, though frequently found in the lumen of the gallbladder and bile ducts in countries where the general rate of infection is high,[8] would certainly not penetrate into a subserosal lymph vessel.

On the other hand, the tissue reaction was identical with the changes caused by necrotic adult forms of Filaria in the epididymis, and the size of the worm agreed with that of the adult of Filaria. It was known that the patient had been infected with Filaria. The examination of the blood before operation showed no filarial forms, but at a subsequent examination, unfortunately three months later, microfilarias were found. This shows at least that the patient was frequently exposed to infection with Filaria. In view of these facts it is certainly probable that the worm was Filaria and that it had gone astray and lodged in a lymph vessel of the gallbladder.

The epithelium of the gallbladder showed a marked capacity for proliferation, proved by the presence of numerous mitotic divisions. Contrary to the assertions of Maximow and Bloom [9] and Weatherford [10] many typical goblet cells were found. The changes of the epithelium certainly form a part of the pathology of the gallbladder which is almost completely neglected by the textbooks of surgical pathology and pathologic anatomy.

As the etiologic explanation of gallstones is still a matter of uncertainty, we refrain from discussing the role of the helminthic infection in the formation of the gallstones in this case; probably the stones were present before the infection occurred.

SUMMARY

The gallbladder of a 28 year old girl suffering from cholelithiasis was surgically removed. Microscopic examination revealed that the mucosa and subserosa were infiltrated with eosinophilic leukocytes, and a necrotic worm was found in a subserous lymph vessel. The worm probably was an adult form of Filaria. There were also interesting changes in the epithelium of the gallbladder.

8. Yang, S. C. H., and Laube, P. J.: Ann. Surg. **123**:299, 1946.

9. Maximow, A. A., and Bloom, W.: A Textbook of Histology, ed. 4, Philadelphia, W. B. Saunders Company, 1942, p. 438.

10. Weatherford, H. L.: A Textbook of Histology, Philadelphia, The Blakiston Company, 1944, p. 387.

TRICUSPID ATRESIA, HYPOPLASTIC TRANSPOSED AORTA AND ASSOCIATED DEFECTS OF A TRILOCULAR HEART

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THE GREAT majority of cardiac abnormalities are discussed by Abbott in her classic work.[1] Variants of recognized cardiac malformations occasionally obtain, however, and complement the entities already described. A rare combination of unusual anomalies in a functional cor triloculare biatrium with tricuspid atresia, persistent ostium primum, transposition of the arterial trunks, hypoplasia of the aorta, coarctation of the aortic isthmus and a pulmonary artery appearing to continue as the descending aorta through a widely patent ductus arteriosus is being reported. A review of the literature fails to reveal a combination of lesions identical with those in the instance being recorded.

REPORT OF A CASE

A 5 day old boy and the first of twins was admitted to the Children's Memorial Hospital, Chicago, because of dyspnea and an epigastric mass palpated twenty-four hours before admission. The infant was full term, was born as a cephalic presentation and appeared normal at birth, weighing 6 pounds and 10 ounces (3,005 Gm.). He had a meconium stool on the first and on the second day of life and was slightly jaundiced on the third day of life. A definite large epigastric mass was felt the day before admission. Respirations were rapid, irregular and grunting, and the infant looked waxy white at that time. He was put in an oxygen tent, where his respiration became more regular. Observations on the blood before admission were as follows: hemoglobin, 116 per cent; red blood cell count, 5,200,000; white blood cell count, 23,600, with the differential count showing lymphocytes 64, polymorphonuclear leukocytes 34, eosinophils 1 and transitional forms 1 per cent; 1 nucleated red blood cell was seen.

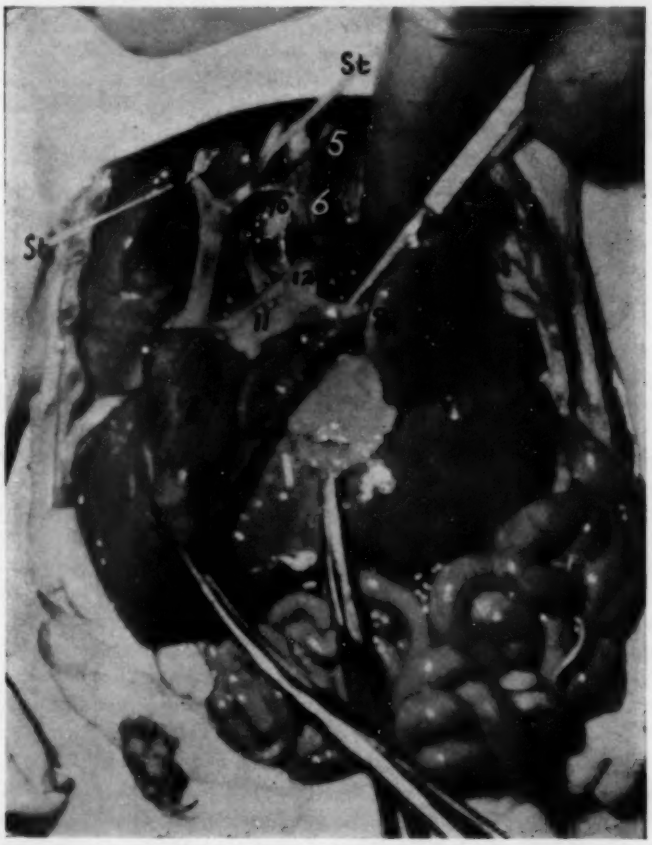
On admission the infant retained a good color apart from the administration of oxygen. There was no apparent jaundice or cyanosis, nor were there petechiae or ecchymoses. The respirations, as stated, were grunting. The lungs were clear. No murmurs could be heard. A mass, presumed to be the liver, was palpated in the epigastrium. Respiratory difficulty became increasingly evident, and despite nikethamide and oxygen the baby died three hours after admission.

Autopsy.—Except for passive congestion of an enlarged liver and patchy fetal atelectasis in lungs evidencing little congestion, the findings of note involved the heart and its great vessels.

From the Otho S. A. Sprague Memorial Institute and the Children's Memorial Hospital, Chicago.

1. Abbott, M. E.: (*a*) Congenital Cardiac Disease, in Osler, W.: Modern Medicine, revised by T. McCrae, Philadelphia, Lea & Febiger, 1927, vol. 4, p. 612; (*b*) Atlas of Congenital Cardiac Disease, New York, American Heart Association, 1936.

The heart lay in the normal position, with the apex directed to the left, and measured 71 mm. from its apex to the summit of the auricles and 35 mm. from the auriculoventricular groove to the ventricular tip. The anteroposterior diameter was 27 mm. and the maximum transverse diameter was 40 mm. A sulcus longitudinalis was not seen externally, though a rounded ventricular hump measuring 14 by 22 mm. was noted at the base of the heart along its left anterior margin. A hypoplastic arterial trunk, subsequently identified as the aorta, arose from this conus-like structure. The epicardial and the endocardial surface were smooth,



The heart has been rotated to the right to visualize the branches of the pulmonary artery and aorta. Note (*1*) the ventricular hump at the left anterior cardiac margin comprising the diminutive outlet chamber for (*2*) the hypoplastic aorta giving rise to (*3*) the innominate artery, (*4*) the left common carotid artery and (*5*) the left subclavian artery. The large pulmonary trunk (*11*) arises to the right of, and posteriorly to, the aorta and gives off the left (*8*) and right (*9*) pulmonary branches. The widened patent ductus arteriosus (*12*) joins the coarctated aortic isthmus (*6*), which continues as the aortic trunk (*7*). The impression is conveyed that the pulmonary artery actually continues as the aorta. Pieces of string (*St*) are tied to the innominate artery (*3*) and the left common carotid artery (*4*) to facilitate identification of the vessels. *10* designates the narrowed aortic arch between the left common carotid artery (*4*) and the left subclavian artery (*5*).

and the myocardium was grossly normal. The right auricle was dilated, bulging upward and to the right, and measured 36 mm. in its widest dimension, with the thickness of its wall measuring 2 mm. Dilated superior and inferior caval vessels and the coronary sinus entered the right auricle in the usual manner and clearly identified this chamber. An interauricular septal defect measuring 5 mm. in diameter opened into an enlarged left auricle, which measured 37 mm. in its widest dimension and carried a small auricular appendage. The left auricular wall measured 2 mm. in thickness. The tricuspid orifice and tricuspid valve were absent, there being nothing to mark the site of the auriculoventricular opening except some thinning at the atretic site. The left auriculoventricular opening was 9 mm. in diameter and was guarded by two distinct valve leaflets, an anterolateral leaflet applied to the base of the common ventricle and a posterior one attached to the auriculoventricular junction at the base of the interauricular septum. The common ventricular chamber was enlarged, its hypertrophied muscle wall measuring 9 mm. in thickness. A thickening of the ventricular musculature was noted at the apex of the ventricle with some suggestion of a ridge marking the anlage of an interventricular septum. An anomalous malposed pseudoseptum composed of a hypertrophied muscle band cut off the small chamber previously mentioned as lying at the base of the common ventricular musculature along its left anterior border. An opening measuring 5 mm. in diameter afforded communication between the common ventricle and its small vestibule. The orifice of exit of the vestibule measured 8 mm. in diameter and was guarded by a tricuspid valve. The thickness of the wall of the small chamber measured 2 mm. A hypoplastic arterial trunk, identified as the aorta by the solitary coronary artery to which it gave rise, issued forth from the small chamber anterior to, and to the left of, the pulmonary artery arising from the common ventricle. The aorta measured 6 mm. in diameter and gave rise to the innominate, left common carotid and left subclavian arteries measuring 4 mm., 3 mm. and 2 mm. in diameter, respectively. The aorta narrowed appreciably after giving off the innominate artery, the aortic arch measuring 2 to 3 mm. in diameter. After giving off the subclavian artery the aortic isthmus measured only 1 mm. in diameter but was joined by an exceptionally wide ductus arteriosus, measuring 10 mm. in diameter, and continued on as the descending aorta. The pulmonary artery issuing from the common ventricle posterior to, and to the right of, the aorta had a tricuspid valve. Emerging from the ventricle, the pulmonary artery was 12 mm. in diameter. The right and left pulmonary arteries were given off from the inferior surface of this large pulmonary trunk, near the pericardial attachment, and entered the hili of their respective lungs anterior to the main bronchi. The pulmonary artery continued through the widened ductus previously mentioned to join the narrowed aortic isthmus. The aortic isthmus joining the widened ductus continued on as aorta, though the impression was conveyed that the pulmonary artery, through its exceptionally wide ductus arteriosus, actually continued as the functional aortic trunk.

COMMENT

A diminutive right ventricle is always associated with hypoplasia or atresia of the tricuspid valve or with a severe malformation of the pulmonary artery in the form of atresia or transposition.[2] Whether tricuspid atresia follows a failure of development of the right ventricle or represents a primary valvular abnormality is of embryologic rather

2. Taussig, H. B.: Bull. Johns Hopkins Hosp. **58**:435, 1936.

than physiologic significance. The heart functions as a trilocular, monoventricular organ or as a biloculate heart, depending on the extent of the interauricular septal defect. Auricular blood empties into a common ventricle and is expelled into the systemic and pulmonary circulations. The hypoplastic outlet chamber, through which some blood is circuited, usually bears the smaller arterial trunk. Inasmuch as the ventricular structure described in the case being reported was combined with a complete transposition of the great vessels (Spitzer type IV) the aorta was hypoplastic and the pulmonary artery large, arising as it did from the main ventricle. Cyanosis was, accordingly, minimal. Indeed, complete transposition of the great vessels in tricuspid atresia is beneficial and compatible with a longer life as it facilitates pulmonary circulation. Hedinger's [3] patient lived into the sixth decade and led a nonrestricted, active existence, exhibiting minimal cyanosis of the lips only on extreme exertion. A single ventricle with a diminutive outlet chamber may also occur in combination with a persistent bulbus cordis or in a more advanced stage of cardiac development in which the aorta arises from the common ventricle and the pulmonary artery from the hypoplastic chamber.[4] In Taussig's [4] cases both great vessels arose from the primitive outlet chamber, while in the case of Glendy, Glendy and White [5] the ventricular and great vessel arrangements were similar to those in the case being described, although not associated with tricuspid atresia or aortic hypoplasia. A left-sided aorta arising anterior to the pulmonary artery also occurs in corrected transposition with bulboventricular inversion in which each trunk is placed in its proper ventricle.[6]

Tricuspid atresia, usually of developmental origin, has been explained as a result of overgrowth and fusion of the endocardial cushions and by an abnormal shift to the right of the interauricular septum sealing the tricuspid orifice. Obliteration of the right auriculoventricular orifice, while the commonest anomaly of the auriculoventricular cusps, is rare among the cardiac abnormalities. Abbott [1b] found only 25 cases in 1,000 instances of congenital heart disease, 9 of which were complicated by transposition or other defects. Some degree of hypoplasia of the pulmonary artery is common, and the ductus arteriosus may accordingly be patent. Sixteen cases were of the "primary" variety associated with a patent interauricular septum and an interventricular septal defect.

Though a right-sided lesion, tricuspid atresia is manifested by left-sided enlargement in the roentgenogram and by left axis deviation in the electrocardiogram. Indeed, it is the only malformation of the cyanotic group associated with left axis deviation.[2] Cyanosis and dyspnea are usually present at birth in the absence of transposition, and increase in severity after the second month of life. Murmurs typical of an interventricular septal defect or a patent ductus arteriosus are inconstant and depend on the relative pressure in the systemic and pulmonary

3. Hedinger, E.: Centralbl. f. allg. Path. u. path. Anat. **26**:529, 1915.

4. Taussig, H. B.: J. Tech. Methods **19**:121, 1939.

5. Abbott,[1b] p. 50, fig. 9.

6. Liebow, A. A., and McFarland, W.: Arch. Path. **32**:356, 1941.

circulation. Hypoplasia of the right ventricle is evidenced by absence of an appreciable cardiac shadow anterior to the aorta in the left anterior oblique position and by exaggeration of the contour in the region of the pulmonary conus occupied by the diminutive chamber.[4] While the shadow cast by transposed great vessels is usually widened in the left anterior oblique position,[7] this would not have been the case in the instance being reported in view of the hypoplasia of the aorta and its displacement to the left. A narrow shadow might have been expected. Dilatation of the right auricle, also presystolic hepatic pulsations in the instance of a relatively intact interauricular septum bearing a small defect, are found in tricuspid atresia. Death ensues within the first year of life in the absence of transposition, though instances have been recorded of the patient's living up to 4 years of age.

Of all the recorded cases of tricuspid atresia, only 1 case resembles, though it is not identical with, the case being reported.[8]

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7. Taussig, H. B.: Am. Heart J. **16**:728, 1938.

8. Wason, I.: J. Tech. Methods **13**:106, 1934.

FATAL RELAPSING FEBRILE NONSUPPURATIVE PANNICULITIS

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SINCE nonsuppurative nodular panniculitis was first described by Pfeifer [1] in 1892 some 30 cases have been reported in the literature, with only two or three autopsy reports.[2] The literature has been amply reviewed by many authors. Because of the confusing clinical picture, the obscure pathogenesis and the scarcity of postmortem reports, the case which we have observed merits publication.

REPORT OF A CASE

About June 1, 1945 a 38 year old Filipino-American corporal began to complain of cough and afternoon fever, for which he was hospitalized in the Philippines on June 8. The history was normal except for malaria in 1937 and thyroidectomy for "adenoma" in 1942. His dietary history was normal. He stated that he did not drink alcoholic beverages. Quinacrine hydrochloride, 0.1 Gm. daily, had been taken prophylactically for the preceding two years.

Except for a temperature of 101 F., examination disclosed nothing remarkable. The white blood cell count was 3,150, and the erythrocyte sedimentation rate (Wintrobe) was 20 mm. in one hour. Blood smears examined for malaria parasites, Wassermann test of the blood, urinalyses, blood cultures, and blood agglutination studies for typhoid and undulant fever gave negative results. Blunting of the right costophrenic angle was seen on roentgen examination of the chest. Examinations of sputum for acid-fast organisms showed no tubercle bacilli.

During the next two and a half weeks he had a daily fever, his temperature ranging between 101 and 104 F.; 480,000 units of penicillin was ineffective. A second white blood cell count was 2,600, while biopsy of marrow obtained by sternal puncture showed essentially normal marrow. Stools were negative for occult blood and for ova or parasites. The basal metabolic rate was + 7 per cent. The prothrombin time (Quick) was prolonged to forty-five seconds (control, twenty seconds). The serum protein was 5.8 Gm. per hundred cubic centimeters.

Between June 27 and July 8 the patient was afebrile. On July 9 his temperature rose to 100.8 F., and roentgen examination of the chest showed small areas of consolidation around the right hilus "suggesting central atypical pneu-

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1. Pfeifer, V.: Deutsches Arch. f. klin. Med. **50**:438, 1892.

2. (*a*) Miller, J. L., and Kritzler, R. A.: Arch. Dermat. & Syph. **47**:82, 1943. (*b*) Spain, D. M., and Foley, J. M.: Am. J. Path. **20**:783, 1944. (*c*) Friedman, N. B.: Arch. Path. **39**:42, 1945.

monia." Sputum examined for tubercle bacilli and fungi again revealed none. Treatment was supportive. Although subsequent roentgen plates of the chest became clear, the patient once more had a daily fever, his temperature rising to 103 F. On July 27 he was evacuated to the United States with a tentative diagnosis of Hodgkin's disease.

During the next four months, while he was a patient at Letterman and Barnes general hospitals,[3] his chief complaints were progressive weakness and a hacking dry cough. He had almost daily elevations of temperature up to 104 F. with frequent frank chills. The physical findings were not otherwise remarkable. The lungs were clear; the heart, normal. Neither the liver nor the spleen were palpable. There was no lymphadenopathy. The skin was clear. Exhaustive laboratory studies were performed. Repeated red blood cell counts and hemoglobin determinations fluctuated between 2,500,000 and 3,100,000 per cubic millimeter and 7.5 and 9.5 Gm. per hundred cubic centimeters, respectively, with transient elevations following transfusions. Eleven white blood cell counts varied between 2,000 and 5,100. Except for a moderate shift to the left, the differential count was not remarkable. Urinalyses showed an occasional trace of albumin. A urine culture was negative. The erythrocyte sedimentation rate was 64 mm. (Westergren) and later 12 mm. (Wintrobe) in one hour. Repeated blood and stool cultures were negative, as were blood smears examined for malarial and other parasites. Blood agglutination studies for Eberthella typhosa H, E. typhosa O, Salmonella paratyphi, Salmonella schottmülleri, Proteus OX2, OX19 and OXK and Bacillus tularense gave negative results, as did skin tests for tuberculosis and coccidioidomycosis. Examination of the blood showed chlorides 495 mg., dextrose 96 mg., nonprotein nitrogen 30 mg. and cholesterol 145 mg. per hundred cubic centimeters. The prothrombin time was seventeen seconds (control, twenty seconds). The serum protein was 5.15 Gm. per hundred cubic centimeters, with albumin 2.58 Gm. and globulin 2.57 Gm. (albumin-globulin ratio, 1). On September 4 the cephalin flocculation was 1 plus in forty-eight hours, and the icteric index was 3. Therapeutic tests with antimony, quinine, penicillin and sulfadiazine were all without benefit. He became progressively worse, and on November 16 he was transferred with condition undiagnosed to the Birmingham General Hospital, Van Nuys, Calif.

On admission into this hospital, and for the first time since the onset of his illness, a cutaneous eruption was noted. Over the flexor and extensor surfaces of both the upper and the lower extremities there were scattered discrete painless nodules measuring from 1 to 2 cm. in diameter. The overlying skin was purplish red and freely movable. The temperature was elevated to 103 F., and the patient appeared toxic and at times lethargic. His response to questioning was slow. Recent loss in weight was apparent. The eyes, the mouth, the throat and the mucous membranes were normal, as were the heart and the lungs. The edge of the liver, smooth and nontender, was felt 2 fingerbreadths below the costal margin. The spleen was not palpable, and there was no adenopathy. The red blood cell count was 3,400,000; the hemoglobin content was 11.5 Gm. per hundred cubic centimeters. The white blood cell count was 2,000, with 68 per cent neutrophils, 30 per cent lymphocytes, 1 per cent monocytes and 1 per cent basophils. Urinalysis showed only an occasional hyaline cast. Repeated determinations of the erythrocyte sedimentation rate showed 7 and 2 mm. in one hour (Wintrobe). Kahn and Wassermann tests of the blood were negative. A roent-

3. Letterman General Hospital is in San Francisco. Barnes General Hospital, closed now, was located at Vancouver Barracks, Wash.

genogram of the chest was normal. Sternal marrow showed nothing remarkable, nor were there any parasites. A nasal smear was negative for lepra bacilli.

On November 28 and again on December 5 biopsies were made of lesions of the skin. Both presented the same picture and will be described at the end of the section on the clinical course.

The patient continued to fail despite further therapeutic trials with quinine, emetine and penicillin. Supportive treatment included transfusions, parenteral

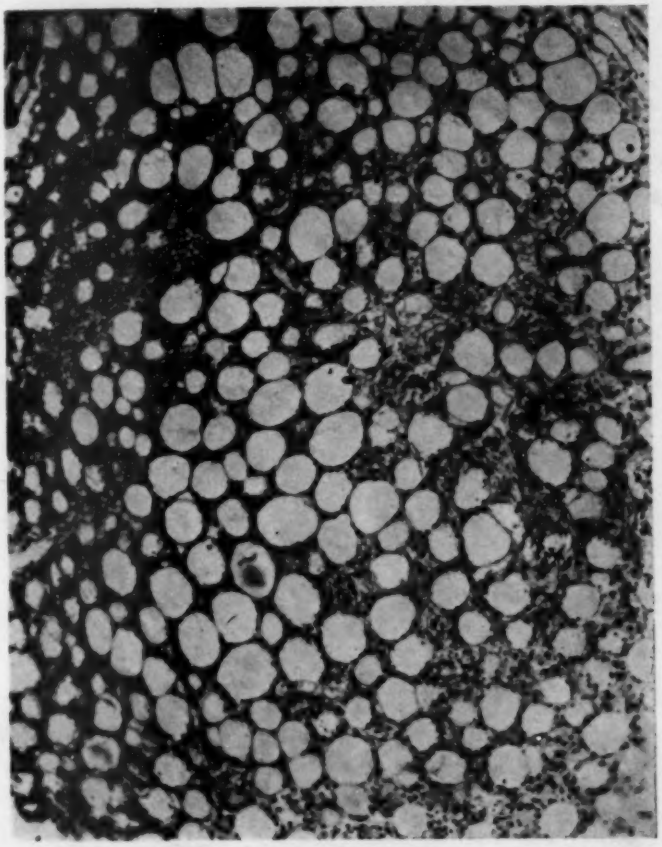


Fig. 1.—Inflammation of fat cells; low power magnification.

injection of fluids and administration of vitamins. He had a daily spiking temperature, reaching 104 F. His hacking dry cough continued. New cutaneous lesions appeared over the trunk and the forehead, while the old ones faded gradually without residual pigmentation or scarring. The liver gradually increased in size, so that shortly before death its edge, smooth and nontender, could be felt 4 fingerbreadths below the costal margin. The spleen was never palpable. There was no icterus. No angioma was seen. Repeated white blood cell counts varied between 2,000 and 5,100. Anaerobic as well as aerobic blood cultures were sterile.

On Jan. 5, 1946, seven months after the onset of his illness, the patient, while asleep, had repeated convulsions lasting several minutes. He could not be aroused thereafter, and three hours later he quietly died.

Report of Biopsy.—The biopsy specimens removed on November 28 and December 5 presented essentially similar microscopic pictures. The sections were stained with hematoxylin and eosin, Giemsa and Ziehl-Neelsen stains. These showed skin and subcutaneous tissue. The epidermis was thin and rather atrophic.

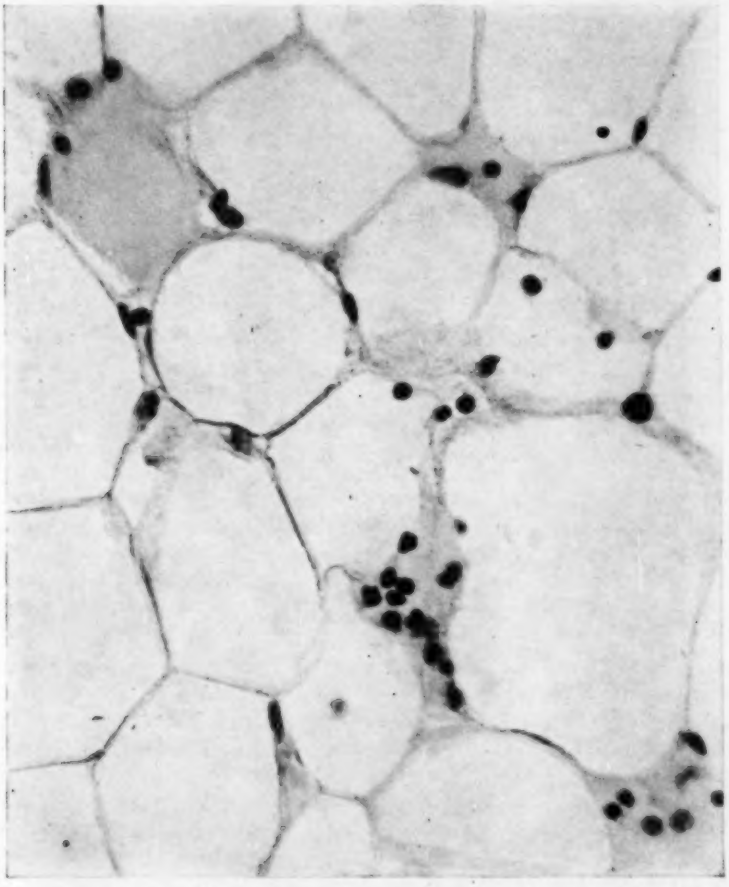


Fig. 2.—Early lesions of adipose tissue.

There was brown pigmentation of the basal layer. Some fibrosis of the dermis was seen. Around the appendages of the skin and elsewhere in the subcutaneous tissue the fat cells showed extensive involvement. The involvement, however, was not uniform. Here and there the fat cells presented an entirely normal appearance with a signet ring arrangement of the cell nucleus and an entirely clear cytoplasm. In a number of fat cells a homogeneously pink-staining material had been precipitated inside the cell membrane. The large majority of the fat cells, however, showed collapse of the cell membrane and partial or complete loss of

cellular outline. These ruptured fat cells were being invaded by varying numbers of foamy macrophages, lymphocytes, plasma cells and polymorphonuclears (figs. 1 and 2).

The inflammatory cells which had invaded the ruptured fat cells tended to arrange themselves in a row immediately within the cell membrane.

Later stages of the process were manifested by necrosis of the adipose tissue and collection of cellular exudate in what apparently constituted a damaged fat cell (fig. 3).

The macrophages were about 20 microns in diameter, had finely vacuolated pale-staining cytoplasm and large round or oval vesicular nuclei. An occasional macrophage contained one or two ingested lymphocytes and an occasional red cell. A few of the macrophages were quite large, but no multinucleated giant cells were seen. No areas of suppuration or abscess formation were found. The inflammatory reaction was occasionally more marked around small-sized blood vessels. In the superficial layers of subcutaneous tissue the inflammatory cell infiltrate was confined to the fat lobules around the appendages of the skin without involving these or the fibrous tissue. It did not extend to the dermis. Nowhere could any microorganisms be seen. There was no scarring.

The diagnosis of nonsuppurative panniculitis was made and confirmed by the Army Institute of Pathology.

Autopsy (six hours after death).—The body was that of a well developed, somewhat undernourished Filipino man, measuring 163 cm. in length and weighing about 65 Kg. There was moderate pitting edema of the lower extremities. A few ill defined, slightly depressed and lighter-colored areas measuring 1 to 2.5 cm. were scattered over the trunk and the face.

There was no icterus of the scleras. The lips were cyanotic. Both parotid glands were considerably enlarged, firm and nonfluctuant. The right parotid gland measured 3 by 3 by 1 cm.; the left, 5 by 6 by 2 cm. The glands were edematous, but no abscesses were encountered. A well healed thyroidectomy scar was present over the neck. The superficial lymph nodes were not enlarged.

The subcutaneous fat measured 1 to 2.0 cm. thick. Grossly, it showed no areas of suppuration, necrosis or nodularity. Section of the breasts revealed no abnormalities.

The peritoneum contained no fluid or adhesions. The surfaces were of normal color and luster.

The pleural cavities each contained about 200 cc. of blood-tinged fluid. The pleural surfaces were smooth and glistening.

The right lung weighed 350 Gm.; the left, 400 Gm. There was congestion, more marked on the left, where a few poorly defined, slightly bulging yellowish granular areas were present.

One hundred and fifty cubic centimeters of clear straw-colored fluid was present in the pericardial sac. The heart weighed 250 Gm. and was grossly normal. The coronary arteries, the aorta, the pulmonary artery and the venae cavae were not abnormal.

The spleen weighed 200 Gm. The cut surface presented a dark bulging parenchyma, in which the malpighian corpuscles were somewhat prominent. Thin sections were obtained with ease.

The liver weighed 2,275 Gm. It had a golden yellow color and was friable. The cut surfaces showed a bulging yellow tissue. There was no fibrosis. The hepatic artery and vein, the portal vein, the bile ducts and the gallbladder were normal.

The pancreas weighed 125 Gm. The duct of Santorini was cystically dilated and measured 1 cm. in diameter. It was filled with granular white material. The main pancreatic duct was normal. No areas of fat necrosis or fatty or fibrous replacement were seen.

Each kidney weighed 125 Gm. The cortices were pale brown and smooth. Coronal sections showed a well demarcated cortex measuring 0.7 cm. The

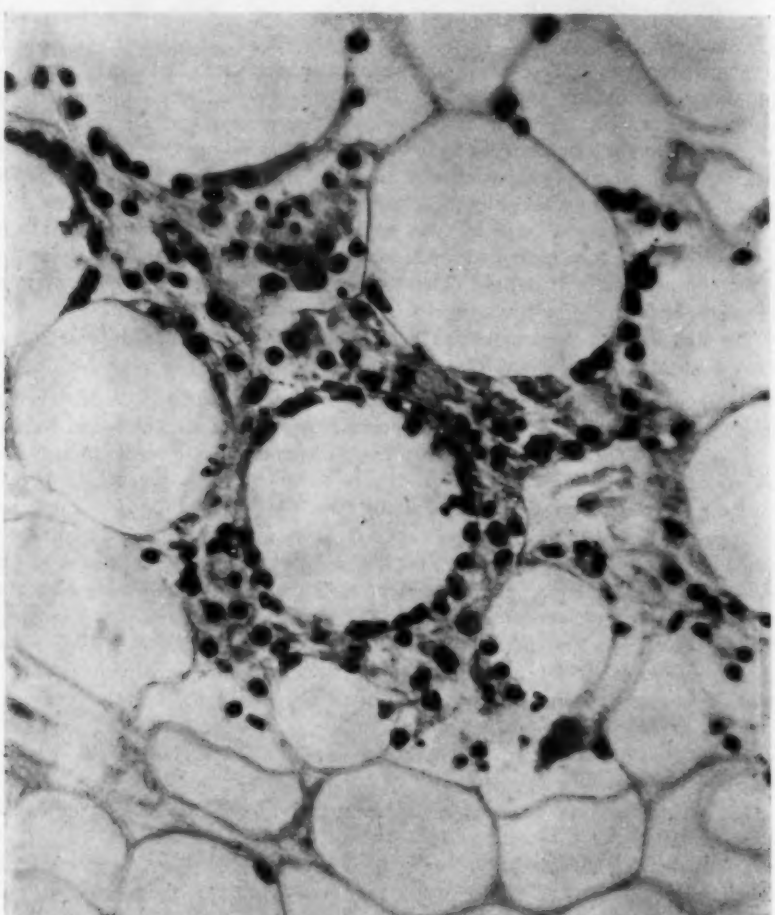


Fig. 3.—Later stages of the lesion. Note the orientation of the lymphocytes inside the fat cell membrane. Several other fat cells are being filled up with the exudate. Note the macrophages.

glomeruli were not prominent. No areas of scarring were seen. The calices, pelves, ureters and bladder and the prostate were normal.

The thyroid gland was almost completely replaced by scar tissue. The parathyroid glands were not identified. The adrenal glands and the pituitary gland were grossly normal. The testes were somewhat atrophic. The lymph nodes were not enlarged, and the cut surfaces were not particularly remarkable. The bone marrow was pale red.

The brain weighed 1,275 Gm. The leptomeninges had a gelatinous consistency. There was a pressure cone at the ventral surface of the cerebellum. The cerebral hemispheres were symmetric. Coronal sections made at 1 cm. intervals showed no abnormalities.

Microscopic Examination.—Routine sections taken from the viscera were fixed in solution of formaldehyde U. S. P. diluted 1:10, embedded in paraffin and stained

Fig. 4.—Skin and subcutaneous tissue with the inflammatory reaction restricted to the subcutaneous fat. Low power magnification.

with hematoxylin and eosin. Gram, Giemsa and scarlet red stains were prepared whenever indicated. The description will be limited to that of the pertinent organs.

Skin: The epidermis was rather thin and somewhat atrophic. There was heavy brown pigmentation of the basal layer. Some hyalinization of the dermis and subcutaneous fibrous tissue was present, but there was no inflammatory cell infiltration (fig. 4). There was considerable involvement of the subcutaneous

fat similar to that seen in the biopsy. In the deeper portions, little inflammatory cell infiltration was present, but as one approached the superficial regions one observed extensive necrosis and infiltration of the fat. No areas of suppuration or abscess formation were seen, and the inflammatory cells consisted of foamy macrophages, lymphocytes and plasma cells.

Liver: There was marked disturbance of the structure by extensive fatty change of the liver cells. The fat occurred in large and small droplets and stained bright red with scarlet red. By and large it had a peripheral distribution. Scattered throughout were areas showing varying degrees of necrosis and hemorrhage. These were seen in midzonal and central areas. In many central areas, however, nests of liver cells were seen with or without some small fat droplets, the cytoplasm of which was sometimes hyalinized and in a few cases showed hyaline bodies. No intranuclear inclusion bodies were seen.

Some of the bile canaliculi were filled with greenish brown bile. There was moderate proliferation of bile ducts, also definite increase in the periportal fibrous tissue. The involved areas were infiltrated by polymorphonuclear leukocytes, lymphocytes, plasma cells and monocytes.

Pancreas: The cystically dilated duct was lined by a single layer of low columnar epithelium. At the periphery of the dilated duct, some atrophy of the pancreatic acini was seen. Little if any dilation of the smaller ducts or of the main pancreatic duct was found. The acinic epithelium had pale, more or less vacuolated cytoplasm, suggesting fatty or hydropic degeneration. The islets of Langerhans were essentially normal. No inflammatory cell infiltration, fatty replacement or fibrosis of the pancreas was present. The peripancreatic and intralobar fat, however, showed considerable inflammatory involvement. The cytoplasmic outline was lost, and the fat cells were invaded by phagocytes, lymphocytes and plasma cells, which arranged themselves inside the cell membrane. Other groups of similar inflammatory cells formed clumps in the necrotic fat cells. The inflammation was closely related to small veins and arteries.

Kidneys: The glomeruli were quite cellular. The increased cellularity was due to endothelial proliferation and some increase of leukocytic infiltration. The afferent and efferent arterioles were sometimes fairly prominent, owing to proliferation of endothelial cells. The tubules showed cloudy swelling and some vacuolation. A few small areas of scarring were seen, in which the tubules were atrophic and contained hyaline casts. The scarred areas were infiltrated by lymphocytes, plasma cells and monocytes.

In the peripelvic adipose tissue several areas of necrosis infiltrated by lymphocytes, monocytes and foamy macrophages were observed.

Adrenal Glands: The cortical cells showed little if any vacuolation. The cytoplasm was pale pink staining. The medulla was normal. There was considerable congestion assuming a hemorrhagic character. In several areas the periadrenal fat showed early involvement, with a few fat cells here and there being infiltrated by lymphocytes and monocytes. No areas of necrosis were present.

Intestines: Sections of the intestines and the mesentery showed several areas of necrosis of fat infiltrated by macrophages, lymphocytes and plasma cells. Occasionally a lymphocyte was seen phagocytosed in a large macrophage.

Heart: Sections of the heart showed similar lesions in the epicardium.

Spleen: The lymphoid tissue was definitely decreased. The malpighian corpuscles were small and indistinct. There was considerable reticulo-endo-

thelial hyperplasia. A moderate amount of golden brown pigment was seen both inside and outside endothelial cells. While a few stem cells were encountered here and there, no appreciable degree of infiltration with immature cells and no hemopoiesis was present. No Dorothy Reed cells or megakaryocytes could be found. The lymph nodes presented similar reticuloendothelial hyperplasia.

Bone Marrow: There was hyperplasia of the marrow with definite retardation of maturity of the granulocytic series.

Postmortem Bacteriologic Study.—Blood culture gave a heavy growth of Bacillus coli.

Final Diagnoses.—Nonsuppurative panniculitis involving the skin, the epicardium and the peripancreatic, periadrenal, perirenal and mesenteric adipose tissue; portal cirrhosis with fatty metamorphosis of the liver; dilatation of the duct of Santorini; hyperplasia of the reticuloendothelial system and the bone marrow; bronchopneumonia; bilateral hydrothorax; terminal acute parotitis; postoperative fibrosis and scarring of the thyroid gland.

COMMENT

This 39 year old Filipino soldier had recurrent fever of seven months' duration, associated with leukopenia and, in the last two months of his illness, with cutaneous lesions that recurred and regressed, leaving no scars.

His history revealed that he had undergone thyroidectomy for adenoma three years previously. Little thyroid gland was left. There was no history of the use of alcohol, tobacco or other drugs.

Prior to his illness he had been given quinacrine hydrochloride for two years, and during his illness he received quinine, sulfadiazine, penicillin and antimony without any apparent change in the course or the outcome of his disease.

The cutaneous lesions observed in this case presented the histologic picture described in other cases reported in the literature and leave no doubt as to the correctness of the diagnosis of nonsuppurative panniculitis.

Miller and Kritzler [2a] were the first to report an autopsy of Weber-Christian disease. In their case the lesions of adipose tissue were limited to subcutaneous tissue. Additional findings were: accumulation of fat in, and focal necrosis of, the liver; hydropic degeneration of the adrenal cortex; phagocytosis of red cells in fixed members of the reticuloendothelial system; fat embolism of the lungs.

Spain and Foley [2b] were the second to report an autopsy. The patient had chronic glomerulonephritis with uremia. Nonsuppurative lesions of the adipose tissue were found in the skin, the mesentery, the omentum and the pretracheal regions. Foci of fat necrosis were seen in the pancreas, but these did not resemble the subcutaneous lesions. No areas of necrosis were found in the spleen or the liver, but there were fatty changes in the latter.

A case has been reported by Friedman [2c] and grouped with these cases by him. The patient had staphylococcic septicopyemia without any visceral lesions of the adipose tissue. The outstanding picture in the panniculus was extensive suppuration caused by staphylococci, and it was quite dissimilar to the microscopic and bacteriologic picture

seen in any of the reported cases of Weber-Christian disease. Therefore, the case may not be considered as representing this syndrome.[4]

Our case showed the most widespread involvement of adipose tissue so far reported in the literature. Nonsuppurative lesions of the fat cells were present in the subcutaneous, epicardial, peripancreatic, periadrenal, perirenal and mesenteric tissue. Hyperplasia of the reticuloendothelial system and of the bone marrow with definite retardation of the granulocytic series was seen. There were foci of necrosis in the liver with portal cirrhosis and extensive fatty metamorphosis of the liver. The duct of Santorini was dilated.

Our patient did not have uremia or any clinical evidence of renal disturbance. There was no fat embolism of the lungs.

The lesions were those of the early stages of the disease, and no scarring was seen.

The genesis of the disease remains obscure. Quinacrine hydrochloride, quinine, antimony, penicillin and sulfadiazine had been given to our patient sometime during the preceding few months. There was a definite element of dietary deficiency. Yet many patients have been seen who have had most of these drugs and been malnourished without panniculitis developing.

It is interesting to note that a tentative diagnosis of Hodgkin's disease had been made early in the course of the disease but could not be verified by histologic examination of tissue. He was also suspected of having leprosy at one time, but nasal smears, as well as biopsy specimens of the lesions, revealed no evidence of this disease. Similarly, no other organisms or parasites could be found in the lesions.

Disturbances of the metabolism of fat present an intriguing explanation, which would be entirely speculative and hypothetic.

SUMMARY

A case of fatal relapsing febrile nonsuppurative panniculitis (Weber-Christian disease) has been presented. This case showed the most widespread involvement of adipose tissue so far reported in the literature. The lesions were in the early stages and involved the subcutaneous, epicardial, peripancreatic, periadrenal, perirenal and mesenteric fat. There was no suppuration, and no etiologic agents could be determined.

4. Since this article was submitted for publication we have seen a report by H. Ungar (J. Path. & Bact. **58**:175, 1946) of a case in which there were widespread lesions of the panniculus showing suppuration and lipogranuloma formation. The patient had chronic streptococcic infection and died of hemolytic streptococcus peritonitis. The outstanding characteristic of the lesions was suppuration due to streptococci. We do not believe that the case should be included under the heading "Nonsuppurative Nodular Panniculitis."

CONGENITAL HYPERTROPHY OF THE NECK OF THE URINARY BLADDER WITH BILATERAL HYDROURETER, HYDRONEPHROSIS AND POLYCYSTIC KIDNEY

ADELE S. VAIL, M.D., and TIMOTHY P. STONE, M.D., FRAMINGHAM, MASS.

CONGENITAL obstruction of the urinary tract is now recognized to be a more frequent cause of hydronephrosis than was thought in the past. In a series of 4,903 autopsies of infants and children, Bugbee and Wollstein [1] noted this condition in 0.9 per cent. The obstructive lesion may be found in either the prevesical or the postvesical tract. Aberrant vessels, strictures of the ureters, ureteral valves, kinks and unusual ureteral insertions are the most frequent causes of prevesical obstruction. Of the causes of postvesical obstruction, it appears that most fall within the category of the urethral valvelike folds, so well described by Young and associates [2] and by Lowsley and Kirwin,[3] which are most frequently found in the region of the verumontanum (colliculus seminalis) and in the posterior part of the urethra. Langebeck [4] is accredited with the first description of the anomaly. Other reports soon followed (Velpeau [5]); it was, however, many years later that a complete study by Tolmatschew [6] had much to do with arousing general interest in the subject. Half a century had hardly passed when Young, Fronz and Baldwin [2] were able to collect 23 similar cases from the literature, to which they added 12 of their own. Six additional cases were reported by Hinman and Kurzmann [7] and 3 by Kretschmer.[8] A search of the literature by Lowsley and Kirwin [3] brought the total number of cases reported up to 1934 to 133, of which 3 were their own. The presence of velamentous valves in the posterior part of the urethra is perhaps the most frequent but not the only cause of postvesical urinary obstruction. Phimosis, stricture of the meatus of the urethra, hypertrophy of the verumontanum and contracture or hypertrophy of the vesical neck have been mentioned occasionally in connection with congenital hydroureter and hydronephrosis. Hypertrophy of the vesical neck has been the subject of an excellent study by LeRoy,[9] who recognized that the condition was due to one or another

From the Department of Pathology, Framingham Union Hospital.

1. Bugbee, H. G., and Wollstein, M.: J. A. M. A. **83**:1867, 1924.

2. Young, H. H.; Fronz, W. A., and Baldwin, J. C.: J. Urol. **3**:289, 1919.

3. Lowsley, O. S., and Kirwin, T. J.: J. Urol. **31**:497, 1934.

4. Langebeck: Mémoire sur la lithotomie, Thesis, Paris, 1802.

5. Velpeau, A.: Nouveaux éléments de médicine opératoire, Paris, J. B. Baillière, 1832, p. 907.

6. Tolmatschew, N., cited by Lowsley and Kirwin.[3]

7. Hinman, F., and Kurzmann, A. A.: J. Urol. **14**:71, 1925.

8. Kretschmer, H. L., and Pierson, L. E.: Am. J. Dis. Child. **38**:804, 1929.

9. Le Roy: Arch. ital. di urol. **11**:175, 1934.

of the following main causes: hyperplasia and hypertrophy of the periurethral glands; hyperplasia of the fibrous connective tissue stroma, most apparent in the submucosa and the muscular coats; hyperplasia and hypertrophy of the muscular fibers; diffuse hyperplasia of all elements of the vesical neck. It is with the latter condition that we are concerned in the case here presented, unusual for the concomitancy of bilateral hydroureter, hydronephrosis and polycystic kidney.

REPORT OF A CASE

A 26 year old secundipara entered the Framingham Union Hospital one month before term after an uneventful pregnancy. Her past history was not relative, and her first child was living and well. In due time labor began and was terminated in a breech extraction. At birth the baby weighed 4 pounds 10 ounces (2,098 Gm.) and measured 12 inches (30.5 cm.) in length. He was cyanotic, and his respirations were "gasping." He was placed in an oxygen bassinet but, despite all attempts at resuscitation, died within one hour and fifty minutes.

Fig. 1.—Urinary bladder, ureters and kidneys, dissected in one block. Note thickening of the neck of the urinary bladder, bilateral hydroureter, hydronephrosis and polycystic kidneys.

Autopsy (Dr. C. G. Tedeschi).—The body was that of a premature baby boy, 12 inches in length and 2,050 Gm. in weight. No evidence of malformation, injuries or lesions of any type was noted with the exception of general cyanosis.

The lungs were atelectatic. About 2 cc. of transparent amber-colored fluid was present in the pericardial sac, but no cardiac abnormalities were observed. The urinary bladder was greatly distended, reaching the level of the umbilicus. The ureters followed a rather tortuous course and were markedly sausage-shaped, owing to alternating dilated and narrowed tracts. The kidneys were greatly enlarged and cystic. The other abdominal organs showed no significant changes.

The kidneys, ureters and urinary bladder were removed together (fig. 1). The right kidney measured 5.5 by 4 by 3.5 cm. and weighed 18 Gm. The left kidney measured 6 by 4 by 3.6 cm. and weighed 19 Gm. The usual structure was completely obliterated by fluctuant saclike formations of different sizes, some of which were empty, while others contained lemon-colored clear fluid. The

calices and pelves were extremely dilated and contained fluid like that in the saccular formations. Each kidney was reduced to a thin layer of tissue from 0.1 to 0.2 cm. in thickness. Tiny cysts were embedded in it. The right ureter measured 7 cm. in length and the left 8.5 cm., and each when opened had a width ranging from 1.0 to 1.5 cm. Both were free from any obstruction. They were lined by smooth gray-pink mucosa.

The urinary bladder measured 6 by 4 by 3 cm. and except for the unusually large size was not remarkable on external examination. It contained about 15 cc. of lemon-colored transparent fluid, and the mucosa was pale gray and glistening throughout. The region of the trigone was clearly made out, and the ureteral openings were promptly recognized. The bladder wall was thickened throughout,

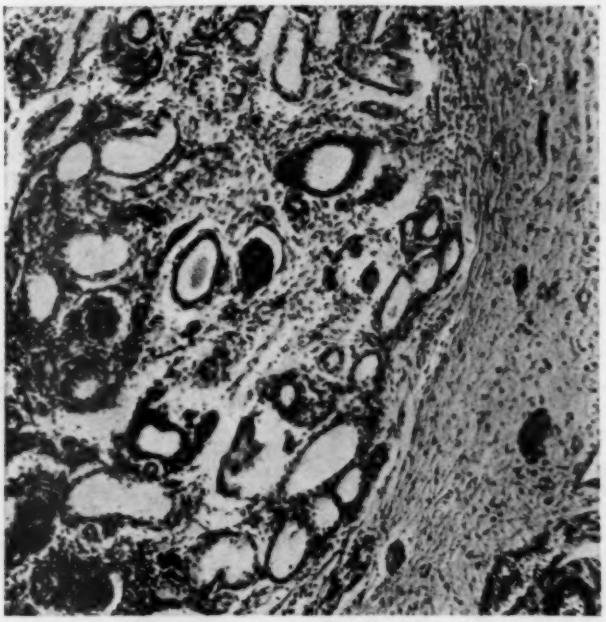


Fig. 2.—Photomicrograph showing an island of epithelial tubules, in disorderly arrangement, embedded in a fibrous stroma in which engorged blood vessels stand out conspicuously (microscope Zeiss, ocular 5, objective 10).

most strikingly in the region of the neck, where it measured from 3 to 5 mm. in thickness. This resulted in marked narrowing of the lumen of the neck, which hardly admitted the finest probe after considerable pressure, regardless of whether the probing was done from the bladder or from the urethra. The latter could be probed without difficulty, and the only pathologic condition in it was hypospadias of moderate degree. Neither testicle was in the scrotal sac.

Sections from both kidneys showed complete obliteration of the usual structure. The most striking pattern was that of islands of epithelial tubules embedded in a fibrous stroma simulating under low power the structure of glandular acini (fig. 2). Some of the tubules were small, and some were dilated into cystic spaces. The smallest tubules were lined by one or more layers of low cuboidal epithelial cells. The cystic spaces were also lined with epithelial cells, which,

however, showed flattening and less frequent stratification. Glomeruli could hardly be recognized; the few present showed striking thickening of the basal membrane of the loops, resulting in a compact appearance (fig. 3). The stroma in which the tubules were embedded was dense and poor in cells in some areas, while in other areas it was loose and edematous, composed of an interlacing of connective tissue fibers, histiocytes and fibroblasts. Engorged capillaries, either isolated or in clumps, were present in the latter areas, and small extravasations of red blood cells were noted. Bundles of smooth muscular fibers were present here and there, pointing, as is generally thought, to immaturity of renal tissue. The calices and pelves were not unusual except for some thickening of the epithelial lining in some places and thinning in other places, with marked vascular conges-

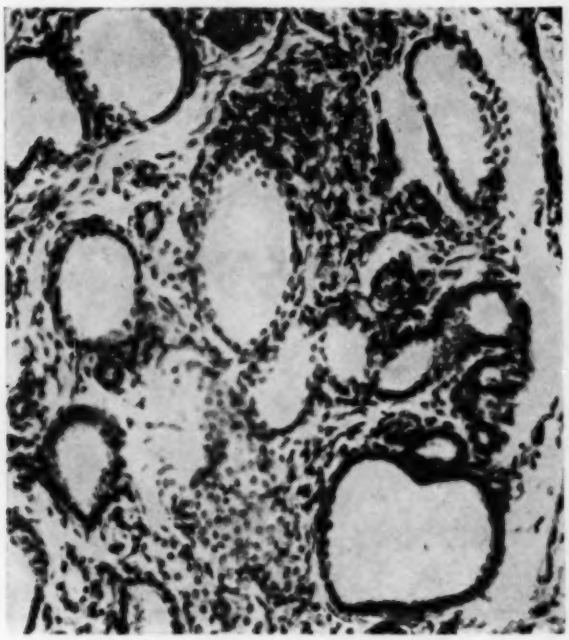


Fig. 3.—Photomicrograph of an area of the same field as that in figure 2, at higher magnification, showing the presence of occasional glomeruli and tubules dilated to cystic dimensions (microscope Zeiss, ocular 10, objective 4).

tion and patchy accumulations of lymphocytes which at times had an arrangement suggesting the structure of lymph follicles.

Changes of the same type were present in the ureters, which in addition showed, deep in the mucosa, small islands of epithelial cells (cell nests of Brunn), some of which were excavated at the center. The thickening of the neck of the urinary bladder appeared in the microscopic sections to be due to a diffuse hyperplasia of all the elements composing the neck. The characteristic disposition in layers and the intimate structure of the muscular fibers were well preserved, but the myofibrils were obviously more numerous and thicker than usual, with scattered evidence of nuclear giantism. Between the bundles of muscular fibers the fibrous stroma was homogeneously thickened, but in no areas was scarring or active inflammatory reaction suggested.

The number of openings of the prostatic tubules into the urethra did not appear to be more numerous than one expects in a premature newborn baby. In sections at different levels, from 34 to 51 prostatic tubules were counted, a number considered to be within normal limits by Lowsley.[10] From the histologic study it was concluded that the cause of the urinary obstruction was diffuse hypertrophy and hyperplasia of all elements of the urinary neck.

COMMENT

The outstanding features of the case can be summarized as follows: bilateral hydroureter and hydronephrosis, polycystic kidneys and thickening of the neck of the urinary bladder, leading to a practically complete urinary obstruction, in a newborn boy. The urinary obstruction in this case falls into the category of "diffuse hyperplasia of all elements of the vesical neck" of LeRoy's classification. An interesting feature of the case is the polycystic kidneys. Giordano [11] published a similar case in which a newborn baby presented ectopy of the heart, extrophy of the urinary bladder, deviation of the spine and left talipes equinovarus. Failure of the involution of the first few generations of the glomeruli and tubules and loss of their connections with the connecting tubules constitute the most favorably accepted explanation of polycystic kidney. Obliteration of the usual renal structure with replacement by adenomatous structures and muscular fibers in the stroma of the parenchyma is evidence in our case also of a deep developmental renal defect.

SUMMARY

A case of systemic malformation of the entire genitourinary tract, with cryptorchidism, hypospadias, hypertrophy of the neck of the urinary bladder, bilateral hydroureter and hydronephrosis, and polycystic kidneys is reported.

10. Lowsley, O. S.: Am. J. Anat. **13**:293, 1912.

11. Giordano, A.: Arch. ital. di urol. **11**:158, 1934.

Obituaries

NEWTON EVANS, M.D.

1874—1945

On Dec. 19, 1945, at Los Angeles, Dr. Newton Evans died of carcinoma of the stomach. Thus ended the career of an eminent pathologist, a pioneer in this field as well as an active exponent of scientific medicine in the West.

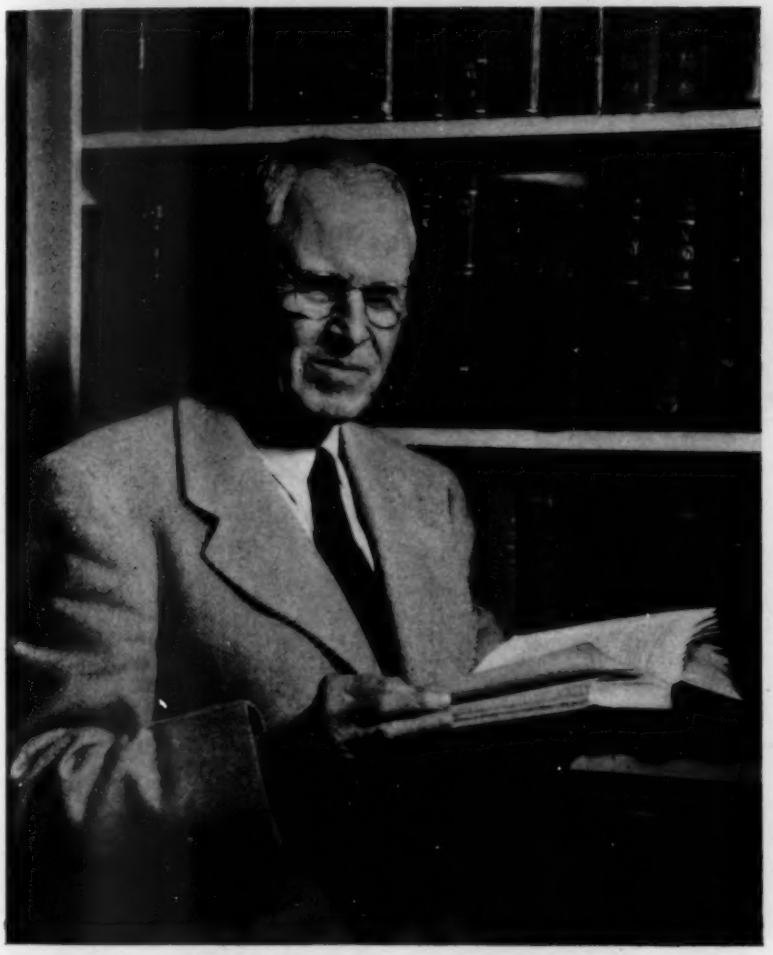
Dr. Evans was born in Hamilton, Mo., June 1, 1874, the son of William and Emma (Newton) Evans. The family moved to Nebraska, where he spent his boyhood and adolescence. He attended Union College at Lincoln, where he received his A.B. degree in 1895. In 1896 he enrolled in the American Medical Missionary College at Battle Creek, Mich., but spent his senior year at Cornell University School of Medicine, where he was graduated in 1900.

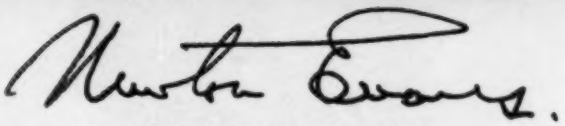
He returned to Battle Creek and began his professional career as an instructor in histology and pathology. Here he was joined in marriage to Cora Mildred Deming. Three children were born to this union, one of whom met an accidental death in adolescence; the two living are Dr. William Dustin Evans and Emma Elizabeth (Mrs. Howard A. Ball). The pressure of mundane obligations forced him to enter private practice in Kentucky and Tennessee for a time, but from 1908 to 1911 he served as professor of pathology and head of the department in the University of Tennessee, where he acquired a reputation as a stimulating and inspiring teacher.

In 1914 Dr. Evans answered an emergency call to a then small and struggling medical school in California, agreeing to teach one course of pathology. When the semester was concluded, he returned to his practice. But his success as a teacher was such that the students unanimously insisted on his return, a call which he found himself unable to refuse. The following year he was appointed professor of pathology and head of that department of the College of Medical Evangelists, a position which he held for about thirty years, his tenure terminating only with his death. During this interval he sponsored and actively promoted the cooperative plan in medical education.

In 1928 he was appointed chief of the department of pathology of the Los Angeles County Hospital. His vision of the place of the laboratory in the field of scientific medicine led to the rapid development of this service, until it became the fountain head of the scientific spirit of the institution as well as the source of help in the solution of the

many diagnostic and therapeutic problems arising in this large hospital. During this interval he was active in many medical and scientific organizations, both local and national. His published contributions





NEWTON EVANS, M.D.

1874-1945

were concerned largely with the rarer granulomatous diseases (torulosis, blastomycosis and coccidioidal granuloma), the pathologic aspects of diseases of the cardiovascular system, the liver and the kidney, and

particularly cancer. His personal interests were thus clearly reflected, for it was his conviction that in the degenerative diseases and in cancer progress must be made if current medicine was to achieve any important progress.

He retired from this position at the Los Angeles County Hospital a short year and a half before his death. He had looked forward to spending his last years as counselor to the administration of the medical school to which he had given much of his time and effort. His death came as a profound loss to the school, one which is still acutely appreciated at a time of rapid and important changes.

Dr. Evans stands out preeminently as a teacher. He was not dramatic or sensational. At times students were inclined to loll at their microscopes—but usually not for long. Questions for idle minds were soon forthcoming. And woe to the student whose lenses were murky and mirror dusty! A lesson not soon forgotten was taught by the professor hmiself, who took the student's place at the microscope, making the optics shine with his own clean handkerchief.

As a teacher he took great interest in the library of the school, becoming its outstanding scientific patron, for he believed that both doctors and students should seek the answers to their questions in contemporary literature.

It was his steadfast, unfailing purpose to awaken interest, to inspire lagging spirits and to encourage the feeble efforts of young men in the scientific way. It may truthfully be said that his own achievements might have been much greater had he not been more interested in seeing others get ahead. The work he was happy to do; the honors he was willing others should have.

Dr. Evans maintained his humble, teachable attitude to the end. Not always easily convinced, he became a forceful supporter of a project when its objectives were made clear and its worth appreciated.

If one watchword would characterize his daily life, it would be "Aequanimitas." His unruffled spirit, his unfailing fidelity and transparent honesty were his way of life. It is this portrait of him that will long live in the memory of his devoted pupils.

CYRIL B. COURVILLE, M.D.